DOCTOR OF HEALTH (DHEALTH)

Pain experience and management during childhood acute lymphoblastic leukaemia

Jensen, Luana Leonora

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Luana Leonora Jensen

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University of Bath

Department of Health

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Abstract

Background

Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer. While most children with ALL survive, pain experienced during treatment is difficult for the children and their family to endure. The aim of this programme of research was to investigate the experience of pain and its management during ALL from the perspective of the child, parents and clinicians.

Methods

A mixed methods approach was used across two studies. In Study 1, perspectives of parents, nurses and doctors in a Danish sample were captured in 16 semi-structured interviews analysed using thematic analysis. In Study 2, six children completed daily diaries of pain ratings using a mobile application during the first three months of their treatment for ALL. The findings from interviews and pain diaries were triangulated through interpretation.

Results

Full data from pain diaries were available in 57.8 % of the sample. In average across all registrations, children reported being in pain 54% (SD =28.77, range 0-100%) of the time. Mean pain intensity was 3.25 (SD=3.4, range 0-10), where 0 was no pain and 10 was the highest level of pain. Paracetamol was reported in 46% (SD= 29.48, range 0-95%) and morphine in 14% (SD= 9.67, range 0-26%) of registrations. Only one participant used other analgesics (tricyclic antidepressants). Non-pharmacological pain relief methods included distraction in 42% (SD= 35.49 range 5-100%), massage in 25% (SD= 34.47, range 2-100%) and a heating pad in 3% (SD= 3.81, range 0-9%) of registrations. Agreement between families and clinicians in symptom severity was more concordant for physical symptoms than for anxiety and emotional distress. There were no differences between mothers' and fathers' perspectives of their child's pain. Parental informational needs were high and family empowerment required individual tailoring. Parents associated opioids with severe illness, whereas non-pharmacological pain relief strategies gave a sense of control and normality. Parental anxiety and child's past pain experiences had a major influence on pain assessment and management.

Conclusion

Pain trajectories in childhood ALL are unique individual experiences. The findings have implications for the need to place a greater emphasis on incorporating the child's voice and in developing broad relief strategies when managing ALL pain.

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List of abbreviations

ALL – Acute Lymphoblastic Leukaemia

APTT - Adolescent Paediatric Pain Tool

BAPQ - Bath Adolescent Pain Questionnaire

FACES - Wong-Baker Pain Rating Faces

FLACC – Face, Legs, Activity, Cry, Consolability

FPS-R - Face Pain Scale-Revised

HCP – Healthcare Professional

IASP - International Association of Study of Pain

NIPS - The Neonatal Infant Pain Scale

NOPHO - Nordic Society of Paediatric Haematology/Oncology

NRS – Numeric Rating Scale

PICU – Paediatric Intensive Care Unit

PTSD - Post-Traumatic Stress Syndrome

VAS – Visual Analogue Scale

WHO - World Health Organisation

WGSR - Word-Graphic Rating Scale

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1. Chapter 1 Introduction

1.1. Overview of Chapter 1

Pain is a common and serious symptom experienced by children with leukaemia (Van Cleve et al., 2004) which is the most common cancer of childhood, accounting for a third of cases (Steliarova-Foucher et al., 2017). Children's adjustment to leukaemia treatment is related to parental support and healthcare professionals´ (HCPs) ability to involve patients and families in the alleviation of symptoms (Bettle et al., 2018). Research presented in this thesis focuses on furthering knowledge about the experience of pain and its management during acute lymphoblastic leukaemia (ALL) from the perspective of the child, parents and clinicians.

To support the development of this knowledge, this chapter sets out the current body of understanding. It opens with a review of the clinical background of this thesis, which begins with a description of pain and its consequences in childhood leukaemia. Pain assessment is then presented, highlighting the importance of self-reporting. This is followed by the presentation of the roles of parents and HCPs in assessing and managing children's pain. The clinical background leads to a presentation of the rationale of the study. This is followed by a clarification of terminology and the final section provides an overview of the organisation of the thesis.

1.2. Clinical background

1.2.1. Pain in childhood leukaemia

Pain is a sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (IASP, 2020). Pain as a signal of threat is particularly distressing in the context of childhood malignancy (Woodgate & Degner, 2003). For many children, pain is an initial symptom that results in a leukaemia diagnosis. Unfortunately, pain continues during the treatment pathway with most children reporting pain as a consequence of chemotherapy and frequent skin-breaking procedures (Van Cleve et al., 2004).

Suffering from ALL and undergoing heavy painful treatments is a very distressing experience for both children and parents (Polizzi et al., 2015). Pain can negatively affect a child's physical and emotional functioning as well as quality of life (Sung et al., 2011) and is associated with parental

post-traumatic stress syndrome (Best et al., 2001). Thus, effective pain management is a vital aspect of paediatric oncology care.

1.2.2. Pain assessment and management

The first essential step in successfully managing pain experienced by paediatric patients is pain assessment (Anderson, 2007). Because pain is a subjective experience (IASP, 2020) the patient's self-report is regarded as the gold standard for identifying the presence of this symptom (Turk & Melzack, 2011). Research emphasises seeking the child's voice in pain assessments (Linder & Wawrzynski, 2018) and various assessment tools have been developed for this purpose (Turk & Melzack, 2011). In this context, the use of electronic self-reported pain assessments has been highlighted in recent studies (Leahy et al., 2018).

Although the child is the one experiencing pain, parents can provide additional perspectives on their child's symptoms and medication (Hedén, Pöder, von Essen, & Ljungman, 2013). Therefore, parental perceptions of a child's pain have a significant influence on assessments and interventions to relieve pain (Tutelman et al., 2019). Furthermore, as leukaemia treatment occurs over years (Toft et al., 2018), HCPs often become familiar with a child's individual characteristics and response to therapy, including their experiences of pain (Linder & Wawrzynski, 2018). Throughout the disease, the successful assessment and management of a child´s pain rely on effective communication and collaboration among children, parents and HCPs (Bettle et al., 2018). However, different patients, clinicians and institutional barriers may impact symptom assessment and management in children (Zhukovsky et al., 2015). Barriers may occur due to differences in the child's ability to communicate their experience of pain (Cheng et al., 2019) or differences in the HCPs' and parents' views concerning illness and treatment (Rosenberg et al., 2014). These views may include various issues, such as understanding symptoms and attitudes toward analgesic medication (Fortier et al., 2012). Moreover, institutional factors may lead to differences in clinicians´ knowledge, pain assessment and management routines as well as family-shared collaboration (Linder & Wawrzynski, 2018).

1.2.3. Rationale for this study

To evaluate the pain of an individual, it is necessary to know the extent of this pain. Accordingly, if a child's pain manifestation is unknown, an understanding of strategies to relieve it may be limited.

The literature provides limited knowledge about pain from the perspective of the child because the use of self-reports in paediatric oncology patients is not yet common (Leahy et al., 2018). However, paediatric self-reports alone may not reflect all aspects of pain. Facing a child in pain elicits a variety of responses in caregivers that may impact the sufferer´s pain (Caes et al., 2017). Therefore, understanding a child's pain is undermined if there is no understanding of how parents and HCPs assess it. Understanding what influences parents' and HCPs' assessments requires an understanding of parental responses to their child´s pain and how HCPs understand these responses. This cannot be ascertained without the knowledge of what parents and HCPs do when they respond. The way in which parents and HCPs respond to a child's pain is a result of various factors, such as the manifestation of the child's pain, cultural background, individual experiences, pain memories, feelings of uncertainty and threatening thoughts of mortality (Finley, Kristjánsdóttir, & Forgeron, 2009; McCaffrey, 2006). The experience of pain involves a child's pain as well as the parents´ and HCPs understanding of it and how the latter respond to it. Therefore, the rationale of this research is based on the close interaction between parent and child and the dynamic interplay between child, parent and clinician in relation to the experience of pain.

Much of the literature investigating how pain presents in ALL utilises different quantitative methods based on child self-reports and parental proxy-reports (Dupuis et al., 2016; Van Cleve et al., 2004). However, in pain research, qualitative methods appear particularly pertinent as they can emphasise the individual differences in relation to subjective experiences (Morse, 2015). For example, qualitative explorations of parents' and HCPs' experiences have been suggested to provide rich data which enables the understanding of a child´s pain (Bettle et al., 2018). Both quantitative and qualitative approaches are useful in pain research and their strengths can be integrated in mixed methods research (Johnson & Onwuegbuzie, 2004). Adopting a mixed methods approach in this thesis, the researcher sought to provide a novel understanding of pain experience in childhood ALL.

1.3. Thesis terminology

In this section, several aspects of terminology will be clarified for the purpose of this thesis. Thus, "parent" refers to mothers, fathers, guardians or any individual with primary caregiving responsibility for a child. A "child" is defined as an individual aged from birth to their 18th birthday. A definition of "home" is any context outside the healthcare setting where pain is not primarily managed by HCPs. Pain "characteristics" refer to pain intensity, frequency and location.

1.4. Organisation of the thesis

This chapter provides readers with the orientation and organisation of the thesis. The first section, clinical background, emphasises that pain is a common symptom in childhood leukaemia leading to negative physical and psychological consequences in the short and long term. Pain assessment is the first essential step to successfully manage a child´s pain. The rationale of this thesis is based on the close interaction between parent and child and the dynamic interplay between child, parent and clinician in relation to pain experience.

Chapter 2 provides a literature review, which aims to ascertain the current understanding of pain in childhood ALL. This chapter reveals areas where knowledge regarding the experience of parents and HCPs with a child's pain in ALL can be extended. Limited evidence exists describing how clinicians perceive a child's and parents' anxiety and distress and how this influences their decisions in pain alleviation in ALL. Furthermore, there is a lack of real-time self-reported pain during the first months of ALL treatment, which are the most stressful. Using the perspectives of different informants involved in a child's care, such as parents, nurses and doctors as well as a child's self-reports of pain may identify different aspects of pain experience in ALL. The literature review leads to the aim of this thesis, which is to investigate the experience of pain and its management during ALL from the perspective of the child, parent and clinician.

Chapter 3 outlines the methodology and the philosophical position for this study. The roles of quantitative and qualitative paradigms in pain research are reviewed. In this thesis, a qualitative approach seeks to explore the perspectives of parents and HCPs on a child's pain, while the child's pain reports are collected quantitatively. In addition, this chapter argues for adopting a mixed methods approach to integrate the qualitative and quantitative findings. The two sets of data are collected at the same time but separately and integrated through interpretation.

Chapter 4 presents Study 1, which seeks to capture the perspectives of parents (mothers and fathers) and HCPs (nurses and doctors) on a child´s pain in semi-structured interviews. This chapter reviews the method and process of data collection and analysis. Ethical considerations and quality in qualitative research are addressed. Using thematic analysis, three main themes were created from the codes generated from the transcripts of interviews.
Chapter 5 discusses the findings of Study 1. Pain evaluation in children with ALL is complex and getting pain assessment right is a challenging process. HCPs emphasised that psychosocial

components played an important role in a child's pain experience. Parental anxiety had a major influence on their child's pain ratings, solicitous behaviour and coping. HCP's concerns referred to best pain management practice and highlighted undertreatment with analgesic medication. This contrasted with parental wishes to avoid opioids whenever possible. Finally, strengths and limitations of Study 1 are presented.

Chapter 6 provides a review of Study 2, which seeks to capture the child's voice using a longitudinal approach during the first three months of ALL treatment. Participants completed daily pain diaries on a mobile application, reporting data on pain and other symptoms related to pain (nausea, constipation, sensory disturbances and muscular strength), the use of pain relief methods as well as the levels of physical activity, general activity and mood. The app was completed by parents of children younger than 10 years while children older than 10 years provided their own data. Ethical considerations in paediatric research are reviewed in this chapter.

Chapter 7 discusses the results of Study 2. These results confirm that pain in children with ALL is common. Although most of the time children had moderate or no pain, they also reported episodes of clinically significant pain during the first three months of ALL treatment. The use of pain medication and non-pharmacological methods reported in pain diaries is discussed. Finally, this chapter provides a discussion of the strengths and limitations of Study 2.

Chapter 8 draws together the results from both qualitative and quantitative parts of this mixed methods study to provide a comprehensive picture of the issues regarding pain experience and management in children with ALL. The combination of data collection methods facilitates the explanation of similarities and differences between a child's self- reports of pain (self-reported by older children or reported by parents of children younger than 10 years) and parental and HCP's views on that pain. In this mixed method approach, the child's voice was used to support the interpretation of parents and HCP's beliefs and practices in pain assessment and management. Chapter 8 concludes the thesis with a description of how this research contributes to new knowledge and implications for both clinical practice and future research.

2. Chapter 2 Literature review

2.1. Overview of Chapter 2

This chapter summarises the literature relating to pain experienced in childhood leukaemia as well as the assessment and management of that pain. Elaborating on the topic of pain, this literature review leads to a presentation of the research question, aim and objectives.

2.2. Leukaemia treatment

2.2.1 Prevalence and Outcomes

Leukaemia is the most common malignancy of childhood, with an annual incidence of approximately 400 cases in the United Kingdom (ChildrenWithCancerUK, 2018). The most frequently occurring type of childhood leukaemia is acute lymphoblastic leukaemia that accounts for 75% of cases (Steliarova-Foucher et al., 2017).

Outcomes for children with ALL have continued to improve over time and have resulted in 5-year survival rates of approximately 90% (Pui et al., 2015). A child who is alive five years after diagnosis is generally considered to be “cured” of the original cancer (Haupt et al., 2007) but some children do relapse (and die) after five years (ChildrenWithCancerUK, 2018).

2.2.2. Treatment protocols

The outcomes in childhood ALL are the results of better care and aggressive anti-cancer therapies delivered according to structured multicentre treatment protocols (Pui et al., 2015). These treatment protocols may be different in terms of anti-cancer medication (e.g. types of drugs, doses or combinations of drugs (Toft et al., 2018).

The research in this thesis was performed in Denmark, where children with ALL were treated according to The Nordic Society of Paediatric Haematology/Oncology (NOPHO-ALL 2008) treatment protocol between 2008 and 2018 (Toft et al., 2018). In this period, the same protocol has been used in Norway, Sweden, Finland, Iceland, Estonia and Lithuania. The results of NOPHO-ALL 2008 are comparable to those from other expert groups, such as the protocols from the United Kingdom, Dana-Farber Cancer Institute, and Dutch Oncology Group protocols (Pieters et al., 2016). During 2019, a new common treatment platform called ALLTogether1-A was introduced in 14 European countries: Denmark, The Netherlands, UK, Belgium, Ireland, France, Portugal, Germany,

Sweden, Norway, Finland, Iceland, Estonia and Lithuania. The purpose of ALLTogether1-A is to improve the overall leukaemia- specific outcome as well as to create a basis for research into the specifics of treatment, disease biology and the continued well-being and quality of life of these patients (Heyman et al., 2018).

2.2.3. Treatment periods

The current chemotherapy protocols for leukaemia outlined in the previous section are lengthy and complex with medications administered over 2.5–3.5 years (Toft et al., 2018). There are three major treatment periods during ALL treatment protocols:

1. The first period is named Induction. Chemotherapy attacks leukaemia cells in the blood and bone marrow to induce remission. Induction is often in hospital and lasts four weeks. The treatment is intensive, and patients experience distressing side-effects from the chemotherapy.
2. Consolidation therapy destroys any leukaemia cells that may still be present. The treatment includes more chemotherapy and sometimes stem cell transplant. Consolidation can take several months and numerous side effects from the chemotherapy may occur. The treatment can be performed in ambulant settings (chemotherapy is administered in hospital as an outpatient) when the patient´s condition is stable.
3. Maintenance therapy prevents any leukaemia cells from growing. This is done using lower doses of chemotherapy than those used during induction or consolidation. Maintenance is continued for up to 2.5 years from diagnosis. During this time, most children are at home and gradually resuming normal activities. However, frequent outpatient visits and tests are required, and side-effects are still present (Heyman et al., 2018). These side-effects will be reviewed in the next section.

2.2.4. Treatment side-effects

Side-effects of chemotherapy are wide ranging and include reductions in physical and psychological wellbeing and autonomy. Pain, nausea, fatigue, lack of appetite, hair loss and drowsiness as well as feeling irritable, nervous, sad and worrying are frequently reported symptoms in paediatric patients with ALL (Hockenberry et al., 2017). Pain is often caused by mucositis (the inflammation and ulceration of the mucous membranes lining the digestive tract causing) that leads to a sore mouth and throat and difficulty swallowing (Kamsvåg-Magnusson et al., 2014). Furthermore, peripheral

neuropathy causes pain, constipation, numbness of fingers and toes, tripping and falling (Anghelescu et al., 2011; Moore & Groninger, 2013).

Besides the administration of chemotherapy with its multiple side-effects, the treatment of ALL typically involves long periods of hospitalisation, frequent outpatient visits as well as numerous diagnostic tests. General anaesthesia is required during frequent procedures such as bone marrow biopsies, lumbar punctures or insertion of central venous catheters. Surgery or other interventions may be needed. Severe cases are admitted to an Intensive Care Unit and may require deep sedation and ventilation. This all results in the substantial burden of morbidity and distress for children and their families and a complex responsibility for the healthcare system (Warner et al., 2015).

2.2.5. Treatment costs

As 5-year survival rates have increased progressively in past decades, it is important to consider the health effects and monetary costs for hospital budgets which are associated with the complex treatment of ALL. Data from literature demonstrates that these associated costs are greatest among paediatric malignancies (Warner et al., 2015). The direct cost per patient to the hospital system include: the ‘hotel cost’ of a hospital stay, nursing, laboratory tests and other diagnostic or monitoring procedures (e.g. radiology), medication and blood products as well as other components of supportive care (Rae et al., 2014). The duration of hospitalisation is an important measure because it is closely linked to morbidity and inpatient care which comprises the largest proportion of the total costs of hospital treatment (Rahiala et al., 2000). In the United States and Canada, leukaemia treatment costs are on average 90.000 USD per patient (Rae et al., 2014). In European countries such as Finland (Rahiala et al., 2000) and the Netherlands (Van Litsenburg et al., 2011), treatment costs are calculated as being more than 100,000 USD per patient. In paediatric oncology, the trend of reducing hospitalisation and increasing the time spent at home lowers treatment costs and improves patients´ quality of life (Hendershot et al., 2005).
Since approximately 80% of childhood ALL cases are long-term survivors, the quality of those surviving years is critical in terms of expense and quality of life representing an investment for the future (Rahiala et al., 2000). Besides financial factors, there is also an ethical interest in reducing the burden of disease and suffering during ALL and minimising the long-term effects of therapy and the additional burdens these bring.

Literature cites pain as the most common and distressing symptom in children with ALL (Van Cleve et al., 2004). Pain continues throughout the treatment trajectory and may persist in long-term survivors (Kelada et al., 2019). The definition and classification of pain need to be addressed prior to considering the issues of pain in children with ALL.

2.3. Definition of Pain

The International Association of Study of Pain (IASP) has recently issued a new definition of pain: "Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." (IASP, 2020). The IASP acknowledges that pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors. Moreover, a person's report of an experience as pain should be respected.

The IASP definition of pain highlights the complex, multidimensional and subjective nature of pain, focuses on individual pain experience, and describes it in a comprehensive way (IASP, 2020). Understanding that pain can occur in the presence or absence of tissue damage supports the fact that pain can be caused by physical as well as by psychological factors (Gatchel et al., 2007). Furthermore, psychosocial aspects of pain may reflect the individual's connection with other people and this influence on pain experience (Williams & Craig, 2016). Thus, pain is more than a single individual's experience as it integrates the subjectivity or "first-person" level of experience of pain, and the challenge for the "second-person" of clinical evaluation (if not also intervention) towards objective "third-person" goals (Cohen et al., 2018).

2.4. Classification of Pain

The IASP defines pain as acute or chronic. Acute pain has a direct relationship to injury or disease, a recent onset, and a possible limited duration of less than three months (IASP, 2017). Acute pain serves as an alert sign to the brain of actual or impeding tissue damage and stimulates the individual to escape or protect the self and avoid further harm in the future.

Chronic pain, recurrent or persistent, is pain lasting three months or more (IASP, 2017). Chronic pain affects a large number of children and adolescents (King et al., 2011) and this chronic pain may continue into adulthood (Soltani et al., 2019). In children and adolescents, chronic pain affects the ability to engage in age appropriate activities and impacts on all areas of life, including self-perception, school attendance, participation in social activities, and sleep (King et al., 2011).

Chronic pain is a prevalent issue among children with certain medical conditions such as juvenile arthritis, sick cell disease and cancer. Cancer, in particular, is associated with high rates of both acute and chronic pain. Cancer pain may be acute when it occurs as a result of diagnostic or therapeutic interventions or chronic when it relates to the progression of disease or treatment (Ljungman et al., 2000). Furthermore, pain in childhood cancer is classified from a sensory perspective as nociceptive, neuropathic or mixed (Howard et al., 2014). Nociceptive pain is described as somatic pain (bone pain or pain due to soft tissue pathology) and visceral pain (e.g. bladder and bowel) whereas neuropathic pain is defined as a pain caused by a lesion or a disease affecting the somatosensory system (Gilron et al., 2015). Understanding the underlying mechanism of pain helps clinicians to develop a more comprehensive approach to managing pain (Casillas & Zeltzer, 2010).

2.5. The Biopsychosocial Model of Pain

The complexity of both acute and chronic pain experiences in addition to the varying importance of different contributory factors (e.g., HCPs, cultural norms, family and peers) have led to the development of different frameworks (models) to better understand the interplay and the role of biopsychosocial factors in paediatric pain (the role of these factors will be specified later in section 2.5.).

The road for the current understanding of pain has been paved by the gate control theory of Melzack and Wall (1965). One of the key implications of the gate control theory and the subsequent neuromatrix theory for researchers and clinicians was the central role of the brain in processing and representing noxious stimuli. The gate control theory, however, was not able to explain several problems associated with the experience of chronic pain, such as phantom limb pain, which require a greater understanding of brain mechanisms (Melzack, 1996). Based on this recognition that pain was more than a sensory experience, subsequent theoretical models broadened their scope to include different mechanisms involved in pain experience like biological factors (e.g., physical injury), cognitive/affective, social and environmental factors (Pillai-Riddell et al., 2013). These models fostered the development of more targeted biopsychosocial models of pain (presented later in this section) which have been used to understand the complexity of pain experiences in both adults and children. This understanding was previously missing but including and placing a greater weight on psychosocial factors in relation to the biological experience of pain expanded the possibilities for intervention.

Further research, particularly findings from in vivo neuroimaging studies have shown that the development and maintenance of chronic pain involve long-term changes in multiple networks in the nervous system, commonly referred to as neuromatrix, which interact in a complex way to contribute to the individual experience of pain (Melzack, 1999). The neuromatrix places affective, motivational and cognitive components within the pain experience and opens up for the understanding of the substantial influence of psychological components on the sensory experience of pain (Turner-Cobb, 2014a).

In children, many of the networks in the nervous system are immature at birth and undergo changes in structure and function during the process of maturation. The neuromatrix includes a genetic template but is also shaped by pain experiences and the psychosocial environment, which add further complexity to the understanding, evaluation, and treatment of pain (Liossi & Howard, 2016; Turner-Cobb, 2014a). This knowledge provides theoretical support for a biopsychosocial model of pain, which is widely adopted as the most heuristic approach to chronic pain (Gatchel et al., 2007). Furthermore, it also provides a background to negate dualistic theories (pain of either a "physical" or "psychological" origin) and justifies a broader and more comprehensive approach (Liossi & Howard, 2016). In addition, there is an increasing focus on the interaction of the social context of pain that includes relationships, social support, family environment, and previous pain experiences, with the individual factors like age and gender and what these bring to the pain experience (Craig et al., 1996). When considering pain in children, the early social context of experiencing pain plays an important role for the future response to pain and explains the potential of psychosocial interventions (Turner-Cobb, 2014a).

There have been several efforts to describe the interactions among biological, psychological and social features/determinants in paediatric pain conditions. In this research study, the design and interpretation were informed by the following paediatric pain models: the integrative model of parent and family factors in chronic pain and associated disability (Palermo & Chambers, 2005), the social communication of pain (Craig, 2009) and the fear-avoidance model (Asmundson et al., 2012). Specifically, in their integrative model of parent and family factors in chronic pain and associated disability, Palermo and Chambers focused on the psychosocial component of the biopsychosocial perspective (Palermo & Chambers, 2005). The authors described different perspectives of parent-child interaction within the broader framework of family systems theories, such as parenting style or parental reinforcement of a child pain behaviours. They proposed that

complex bidirectional relationships exist between family variables and chronic pain in children, which would impact on family dyadic interactions and the overall functioning. Palermo (2012) extended this model by adding further biological, psychological and social components. The biological processes included genetic factors, sex and maturation. The psychological variables highlighted individual beliefs, coping, mood, anxiety and fear while social variables focused on the school environment, culture and characteristics of the healthcare system. The key elements of the Palermo model that informed this research were firstly the impact of family variables on bidirectional child-parent interactions and secondly developmental factors like child's age and maturation.

An important framework that influenced this research is the social communication model of pain, which considers the broader social ecological systems within which the child's pain is experienced (Craig, 2009). According to this model, the interaction between the child and the individuals in the child's environment follows four stages: 1) the child experiences pain, 2) the child expresses pain, 3) a caregiver assesses child's pain and 4) actions taken or not taken by others that would impact on the child´s pain. In this model, the central components are the child's pain expression and the caregivers' assessment of this pain. This is particularly important in paediatric pain as children rely on their parents, HCPs and other adults for caregiving including the assessment and treatment of pain. The key element of this model that informed my research was the social context where a child's pain was expressed, assessed and responded to. Applying a biopsychosocial framework allowed an extension beyond the clinic to the home context and the relationships between the two contexts were crucial. Thus, this model linked to the pain treatments given, capturing pain management both in hospital and at home where parents provided a range of actions in response to the child's pain.

The fear-avoidance model is another concept that has informed this research (Asmundson et al., 2012). This model emphasises the reciprocal influences of child and parent factors in the development and maintenance of chronic pain. Specifically, this model illustrates the bidirectional relationships between parental pain management behaviours (e.g., protectiveness, solicitousness), parental psychological responses (e.g., catastrophising about child's pain, anxiety, distress) and the child's psychological responses (e.g., acceptance, anxiety sensitivity) in influencing the child's escape and avoidance behaviours. The key elements of this model that informed this research were

the parental psychological responses to a child's pain (anxiety, distress) and the child's psychological responses (anxiety, acceptance, coping).

The next sections will present several biological and psychosocial factors that underlie the individual variations in pain perception and response to pain.

2.5.1. Genetic influence

Studies of human genetics indicate that pain perception is influenced by a person's genes. Genetic factors may contribute to individual differences in pain sensitivity and risk of developing clinical pain conditions (Tremblay & Hamet, 2010). In addition, an individual's genetic predisposition plays a role in their responses to opioid dosages, thus affecting the therapeutic doses of morphine for patients with pain (Sadhasivam et al., 2014). However, clinical tools to assess genetic factors are not yet available and more research is needed to enable clinicians to individualise their therapeutic pain strategies (Tremblay & Hamet, 2010).

2.5.2. Developmental factors

Existing research suggests that a child's age and gender are important factors in the onset and experience of chronic pain. Paediatric chronic pain increases with age and peaks in adolescence (Roth-Isigkeit et al., 2005). Research on pain prevalence suggests that females are more often affected by chronic pain than males (King et al., 2011). In longitudinal studies of children with cancer, research has also evidenced support of higher levels of pain and distress in older children compared to younger ones. These results were reflected in both child and parental reports (Van Cleve et al., 2004) as well as in nurses' evaluations (Van Cleve et al., 2011). Moreover, older children with leukaemia were more likely to receive opioids during leukaemia treatment (Getz et al., 2018). However, these findings were questioned in another study that found no difference in symptom burden associated with a child´s age (Hedén et al., 2013).

In contrast, studies of acute pain related to procedures like blood tests found higher ratings of pain and anxiety in younger children (Fradet et al., 1990). Parental prediction of how upset the child would be before procedures was a predictor of the observed distress and self-report of pain. Consistent with this idea, parents of preschool children were more likely to report that their child experienced procedure and treatment related pain and anxiety during the treatment pathway of ALL (Dupuis et al., 2016).

Regarding a child's gender, research suggests there are no gender differences in pain and distress in children undergoing painful procedures, such as catheter insertion (Badr et al., 2006) or lumbar punctures (Walco et al., 2005). However, a significant difference by gender in coping strategies was reported by Van Cleve et al (2004) in older children with ALL with females reporting they had more coping strategies than males. Moreover, girls with ALL exhibited a higher sensitivity to pain measured on morning salivary cortisol level and sensitivity scales (Firoozi & Rostami, 2012). In addition, female gender and age were associated with a lower quality of life during ALL treatment (Eiser et al., 2017; Sung et al., 2011).

Research suggests that a child's experience of pain may be influenced by age and gender along with other factors like culture and ethnicity.

2.5.3. Culture and ethnicity

Cultural expectations and social norms learned in childhood may influence reports of pain and encourage avoidance or acceptance of pain by children (Gharaibeh & Abu-Saad, 2002). Consequently, children will respond according to learned examples of behaviour. In some cultures, a certain behavioural response to pain like crying may be rewarded by cuddling, whereas in other cultures this same behavioural response may be ignored or punished (Jongudomkarn et al., 2006).

In addition, the literature indicates that race and ethnicity may contribute to the severity of symptoms in children (Fortier et al., 2009). For example, Myers et al found that Hispanic children with ALL were more likely to experience symptoms of anxiety (Myers et al., 2014) whereas other studies did not report differences in pain and anxiety due to race and ethnicity (Dupuis et al., 2016; Pfefferbaum et al., 1990). Though the evidence is limited with regard to cultural implications of pain assessment in children, the experience, expression, and reaction to pain are affected by the culture the child is brought up in (Jongudomkarn et al., 2006). Thus, focusing on children's pain without taking into account their culture and family beliefs can lead to inadequate assessment and management of paediatric pain (Finley et al., 2009).

2.5.4. Previous pain experience

The previous experience with pain is, among other factors, a predictor of the child's current pain experience. Pain sensitivity is heightened when children are repeatedly exposed to painful stimuli, and negative previous experiences are likely to reoccur in subsequent painful circumstances

(Bournaki, 1997). Therefore, children with leukaemia who had experienced pain and anxiety during lumbar punctures, were at risk of experiencing higher pain levels during subsequent procedures, indicating that children's memories played an important role in their experience of distress (Chen et al., 2000). This emphasises that management of pain and anxiety is important every time a child undergoes a potential painful treatment to avoid a subsequent increased pain response.

In summary, there is evidence that the child's perception and response to pain are influenced by several biological, psychological and social factors that include: genes, age, gender, culture, ethnicity and a child's previous experiences of pain. Furthermore, parents play a key role in a child's pain care and the influence of parental anxiety and distress on a child´s pain experience will be reviewed next.

2.5.5. Parental distress and coping

There is a growing body of research in general acute and chronic pain, which investigates parental responses to children´s pain and the influence of parental behaviours on the functioning of children with pain. In particular, pain catastrophizing has emerged as an important factor associated with maladaptive emotional, behavioural, physiological and interpersonal responses to chronic, acute and experimental pain across lifespans (Quartana et al., 2009). Parents who engage in greater catastrophic feelings regarding their child's pain seem to experience increased distress and greater likelihood of wanting to reduce the level of activity of their child (Langer et al., 2009). Other studies have found that certain parental characteristics, such as personality traits (e.g., increased anxiety) and certain types of parental behaviour, such as solicitous behaviour, influence the perception of pain in children. For example, Peterson and Palermo (2004) found parental solicitous behaviours to be associated with higher functional impairment among children with greater psychological distress. Furthermore, parental anxiety has been associated with paediatric pain severity and levels of impairment (Tsao et al., 2006).

Similar to other conditions with chronic pain, parental anxiety is associated with pain-related disability in children and adolescents with cancer (Link & Fortier, 2016; Tutelman et al., 2019). Parental anxiety significantly predicts solicitous behaviours and influences a child's pain and quality of life. Nevertheless, there are differences between having a child with a benign chronic condition and the issue of a life-limiting diagnosis. The diagnosis of cancer leads to an existential shock for parents, who experience numerous challenges such as trying to manage their child's

disease. These challenges may include: seeking information and trying to access support from people in their network, (Ljungman et al., 2003), facing socioeconomic problems (Mader et al., 2020) and dealing with strong emotions like fear and worry (Holm et al., 2003). The literature demonstrates that parents experience severe distress during a child's disease and post-traumatic stress syndrome (PTSD) symptoms are found in a considerable portion of parents years after diagnosis (Norberg & Boman, 2008). These findings are consistent with those of Kazak et al (2004), who found that nearly 20% of families with a childhood cancer survivor had at least one parent with current PTSD.

The paediatric leukaemia literature has demonstrated that high levels of parental anxiety during a child´s disease are a significant predictor for the child's level of distress (Caes et al., 2014) and parental PTSD symptoms (Best et al., 2001). Therefore, adjusting and coping with a life characterised by challenges and distress is not only the purpose regarding changes in their lives, but also the means by which these parents achieve this (Brown et al., 1992). Qualitative literature in this area has shown that parental coping significantly predicted children's experience of the severity of symptoms and quality of life, which in turn predicted parental trust in the medical care given. Furthermore, the parental response to the perceived vulnerability of the child, and the former's need to give meaning to parenthood, influenced the child's perception of his/her life, the child's ability to cope and willingness to undergo treatment (Tremolada et al., 2005). However, parental experience with a child's illness may differ, depending on their gender and the participation of mothers and fathers in paediatric research will be discussed in the next section.

2.6. Mothers and fathers

Previous paediatric research has mainly focused on maternal roles and influences on children with chronic illness. The literature demonstrates that research lags behind in including fathers in research design (Phares et al., 2005). Some studies have only included mothers (Earle et al., 2007; Tremolada et al., 2005). Other studies have targeted both parents, but maternal participation was dominant (Eden et al., 1994; Jordan et al., 2007).

Research found that mothers and fathers differed in their experience of and response to parenting a child with cancer. These differences appeared to reflect traditional parenting roles characterized by a gender-based division of labour (Elliott Brown & Barbarin, 1996). In contrast to these findings, other studies suggested that fathers wanted to be engaged in daily functioning and treatment

decisions with the aim of bringing a sense of normality during ALL treatment (Hill et al., 2009; McGrath & Chesler, 2004a). Moreover, fathers acknowledged expressing feelings and worries although they preferred "actively doing" rather than attending to the emotional aspect of the experience (Hill et al., 2009). These findings challenged the notion of stereotypical gendered coping styles, suggesting that coping responses were not based upon gender but rather on each partner's strengths and weaknesses (McGrath & Chesler, 2004a).

In summary, fathers as well as mothers play an important role in the emotional and behavioural functioning of their children and the literature emphasises the need for studies to include fathers in therapeutic and research activities (Phares et al., 2005). Both parents assume caregiver responsibilities and trust in medical care is central to managing a child's disease. This theme will be elaborated upon in the next section.

2.7. Communication between families and HCP

Children with ALL and their parents face complicated treatment protocols with various medicines and distressing side effects. The child's medical team may be viewed as a source of support and comfort during the diagnosis and treatment. The relationship between parents and HCP or other parents in a similar situation is very important as parents experience a form of social isolation during the child's disease (Ljungman et al., 2003). During the treatment pathway, parents move from being initially overwhelmed on diagnosis to learning what they need to know to manage child's condition (Sawyer et al., 2000). Developing trusting therapeutic relationships between HCP and parents may help families navigate through the experience of illness (Bettle et al., 2018).

Parents perceive themselves as having the main caregiver responsibility and have a strong desire to support their child (Tremolada et al., 2005). Parental involvement in their child's care is better supported when parents are considered equal partners and valued for their expert knowledge of their child (MacKay & Gregory, 2011). When present, concordance between parents and HCPs' expectations regarding treatment and prognosis is associated with a better patient quality of life and improved care. Therefore, it is essential that HCPs support and inform parents as fully and as clearly as possible regarding all aspects of disease and its management (Rodgers et al., 2016). Parents prefer information through clear communication to enable choices and options and want to learn about self- management therapies (e.g. cope with child´s pain). (Ljungman et al., 2003). Parents have a strong need for information and this need takes precedence over issues of emotional

or family impact issues (Pyke-Grimm et al., 2007). However, the emotional state of the parents determines their ability to hear and comprehend the information given (Eden et al., 1994). Therefore, it is important that HCPs understand and inform these families according to their needs and priorities (Zhukovsky et al., 2015). Increased direct physician–patient communication, as well as the proactive discussion of emotions, physical symptoms and quality of life may enhance communication and ultimately, meet the informational needs of families (Levine et al., 2019). A priority for children and parents is the discussion of symptoms including pain. Pain characteristics in ALL will be discussed in the next section.

2.8. Pain characteristics in childhood leukaemia

Pain is perceived as one of the most problematic symptoms experienced during ALL (Van Cleve et al., 2004). Children with ALL experience multiple sources of pain during their disease. This pain is often categorized as: 1) Treatment related pain, e.g., pain related to chemotherapy or radiation 2) Procedure related pain, e.g., pain due to lumbar puncture, bone marrow aspiration, venous puncture or postoperative pain 3) Pain related to the disease, (e.g., infiltration of various organs and tissues).

Many children with ALL begin their experience with pain related to the disease, such as severe musculoskeletal and abdominal pain. In addition, treatment protocols induce and maintain pain related to numerous side effects and procedures (Toft et al., 2018). Among these procedures, lumbar punctures and bone marrow biopsies (Zernikow et al., 2005) as well as venous punctures and central line accesses are considered very painful (Badr et al., 2006; Spagrud et al., 2008).

Pain during ALL is documented in a 1-year longitudinal study (Van Cleve et al., 2004). This study found that most children regardless of age (4-17 years) experienced significant pain during seven data collection points. The most common pain locations included legs (26.5%), abdomen (16.6%), head/neck (16.6) and back (14.2%). These pain locations are frequently associated with medical procedures and chemotherapy drug effects. Leg pain is often related to administration of vincristine, which causes neuropathic pain (Moore & Groninger, 2013). Most children (90%) experienced pain at diagnosis and 60% one year into treatment. Consistent with these findings, Dupuis et al (2016) found that pain due to the disease predominated in the beginning, whereas treatment related pain was more problematic with continued therapy. In this study, parents of children aged two to 10 years reported children´s pain and anxiety at one, six and twelve months after diagnosis. Younger children felt more procedure-related anxiety and focussing on both pain and anxiety may help target

both symptoms. Furthermore, Hockenberry et al (2017) found that pain was a significant contributor in symptom trajectories along with sleep problems, fatigue, nausea and depression during the first 18 months of ALL treatment (Hockenberry et al., 2017). Data was collected at four various points from children aged three to 18 years old. Parents completed symptom assessments for younger children, whereas children seven years and older provided self-reports. Although the burden of disease improved during treatment, the symptoms related to treatment continued throughout the study period.

Several studies have looked at the prevalence of pain in children with ALL depending on the stage of treatment and found that pain was highest at the beginning of treatment trajectories. For example, Gedaly-Duff et al asked children to keep pain diaries, parents to complete questionnaires and both to wear wrist actigraphs to measure pain, sleep and fatigue. They found pain and sleep disturbances throughout the first three days following chemotherapy (Gedaly-Duff et al., 2006).

Other studies have focused on the setting, whether the children were in hospital or at home. Most research investigates children in both settings (Van Cleve et al., 2004). However, as outlined previously, there is a significant focus on outpatient treatment models due to lower treatment costs and the higher quality of life for the patient (Hendershot et al., 2005). Therefore, the care of children with ALL has transitioned from inpatient to outpatient settings, placing parents in a position where they are frequently responsible for assessing and managing their child's pain (Fortier et al., 2014).

Children´s multiple pain experiences are stressful and may contribute to distress and anxiety for both parent and child (Best et al., 2001). Research indicates that children experience considerable emotional distress in the immediate postdiagnosis period (Sawyer et al., 2000). The frequency of anxiety is elevated at the end of the first month of therapy, but then declines to levels expected in a normative population at six and 12 months after diagnosis. In contrast, depressive symptoms are considerable from the end of the first month of therapy to 12 months after diagnosis (Myers et al., 2014). Furthermore, children on therapy for ALL have a lower quality of life compared to healthy children and this is constant throughout different treatment phases (Sung et al., 2011).

In summary, although studies focus on different outcomes, measures and populations, there is evidence that pain is a common and serious problem for children with ALL and this pain affects physical and emotional functioning. The next section will focus on methods of pain assessment.

2.9. Methods of paediatric pain assessment

Different methodologies can be used to identify and assess the experience of pain in children: physiological, behavioural or observation and self-reporting.

2.9.1. Physiological pain measures

For non-verbal children (e.g., children with a developmental language disorder) or sedated children, pain can be assessed by physiological parameters, which include heart rate, respiration rate, cortisol levels and blood pressure. These physiological responses, like behavioural measures, reflect a generalised and complex response to pain and to stress (Turk & Melzack, 2011).

2.9.2. Behavioural pain measures

Other methods of assessment of pain include observation of facial expressions (direct or indirect via video) (Vervoort et al., 2009) or observations of a child's behaviour (Turk & Melzack, 2011). Behavioural scales support clinicians to record how children respond when they experience pain and document any behaviours that seem caused by pain. Signs of distress observed in many children are hence categorized as pain. However, the responses looked for may vary with the developmental stage of the child. For example, older children may become very still while young small children may show discomfort and cry (Cheng et al., 2019).

Behavioural pain scales include several items, which identify different behavioural aspects associated with pain responses. These items are scored on a 0-2 or 0-4 scale, then added to produce a composite pain scale often from 0 to10 (Turk & Melzack, 2011). Behavioural pain scales are frequently used for procedural or postoperative pain assessment in small children (Moutte et al., 2015). Examples of these scales are: Face, Legs, Activity, Cry, Consolability (FLACC) scale 0-10, which is used in children younger than five years (Merkel et al., 1997) and the Neonatal Infant Pain Scale (NIPS) that is specifically developed to assess neonates (Lawrence et al., 1993). During the last two decades, pain scales have been tested and adapted for non-verbal children (Herr et al., 2006). FLACC scale is one of the scales that has been studied and can be applied for children with special needs (Voepel-Lewis et al., 2002).

2.9.3. Psychological pain measures

Psychological pain measures include a broad spectrum of techniques to capture the subjective experience of pain such as questionnaires, qualitative descriptive and quantitative rating scales. Projective techniques allow children to express their feeling about pain through drawings, colours and interpretation of cartoons (Sadruddin & Hameed-ur-Rehman, 2013). Although these methods are useful for both verbal and non-verbal children, the practical application may be challenging and there are no available guidelines on the age-appropriate interpretation (Turk & Melzack, 2011). Research has mainly focused on methods that facilitate standardised patient self-reporting, which can provide valuable information about disease and treatments. In addition, these measures can be used in the clinical setting to diagnose and monitor painful conditions.

Self-report pain measures

Interviews with children are ideally the best method to understand their pain and the factors that influence it. Short interviews are, in a flexible way, a part of the clinical examination of the child. Moreover, for research reasons, several structured and semi-structured interviews have been developed to assess children's knowledge on pain and the language they use to express it (Docherty & Sandelowski, 1999). One method used to assess paediatric chronic or recurrent pain is the Varni/Thomson Paediatric Pain Questionnaire (Varni et al., 1987), which can capture information about a child´s sensory, affective and evaluative dimensions of pain.

Pain intensity rating scales

The intensity of children's pain experience can be quantified on several pain scales. Children can be asked to choose a level on such a scale that best matches their pain. It may be a colour on a Visual Analogue Scale (VAS) 0-10, where "0" is no pain and "10" represents the worst imaginable pain (McGrath et al., 1996). It may also be a number on a Numerical Rate Scale (NRS) 0-10 or a word from lists describing different intensities such as Word-Graphic Rating Scale WGSR (Tesler et al., 1991). Children can also choose a face from a series of faces varying in emotional expression on Bieri Faces scale (Bieri et al., 1990), on Face Pain Scale-Revised (FPS-R) (Hicks et al., 2001) or Wong-Baker Pain Rating Faces (FACES) (Tomlinson et al., 2010)

These self-report scales are easy to use, but no single scale seems to be optimal for use with all types of pain or across the developmental age span, therefore age-based tools have been developed

(Turk & Melzack, 2011). Visual and coloured analogue scales are ideal for children older than five (McGrath et al., 1996). Numerical scales can be used by school children while Faces scales can be used to provide self-reports for children four years and older (Tomlinson et al., 2010). Moreover, there are methods developed for adolescents, such as the Adolescent Paediatric Pain Tool (APPT) (Jacob et al., 2014) and the Bath Adolescent Pain Questionnaire (BAPQ) (Eccleston et al., 2005).

Electronic pain assessment

Pain rating scales are now available on mobile applications on smartphones and tablets. There is a strong correlation between paper and electronic pain scales but most children prefer the electronic version (Wood et al., 2011). The use of electronic diaries to collect real-time data has been shown to improve the accuracy of symptom tracking and pain relief monitoring as these applications are readily accessible and patients can report their symptoms in the moment, rather than having to attempt to remember these symptoms later (Wesley & Fizur, 2015).

Electronic diaries developed as mobile applications on iPhone, Mobile Oncology Symptom Tracker and Pain Squad have been tested in adolescents with cancer for three weeks (Baggott et al., 2012) and four weeks respectively (Jibb et al., 2017). The completion rates were high and at the end of the studies, the users reported that the applications were easy to use. While these two studies presented a remarkably high response rate, they only covered short periods of time, which may have inflated the reported completion rates. The literature regarding electronic pain diaries indicates that completion rates are positively associated with shorter diaries, financial compensation and using an alarm (Leahy et al., 2018; Morren et al., 2009).

A picture of daily symptoms and pain relief strategies in childhood leukaemia during the first months of treatment, which are most stressful, would provide a more nuanced picture of a patient´s disease and reactions to treatment. Collection of electronic self-reported pain data provided by parents or older children throughout several months of ALL treatment has not been done before. In addition, this would illustrate the challenges met by patients involved in long-term electronic self-monitoring of symptoms.

Although caution must always be used when interpreting children’s pain solely from pain scales, it seems useful to use these scales in evaluating painful conditions and procedures and pain relief interventions (Gordon et al., 2005). The registration of variations in pain intensity is also important in the diagnostic process itself. A graded scale is necessary because pain treatment may be effective

even without eliminating all pain. In addition, assessment and reassessment of pain facilitates treatment and communication among clinicians.

2.10. The use of pain assessment methods by HCPs and parents

Despite recommendations and the availability of several pain assessment methods, reports indicate that validated measures of pain in children (e.g., VAS, NRS, FLACC or Faces scales) are infrequently used. Therefore, studies of pain management practices in hospital found that a significant proportion of children did not have pain recorded in the first postoperative 24 hours and children´s behaviour appeared to influence nurses' pain assessment more than validated scores (Twycross, Forgeron, et al., 2015). Similarly, physicians seldom used pain intensity scales in children in an emergency department, especially in children younger than eight years (Moutte et al., 2015). The use of pain scales was also found infrequent in paediatric oncology, which was not consistent with local guidelines (Plummer et al., 2017).

When considering parental assessment of a child's pain, studies generally refer to the postoperative period. Teaching parents to use a pain assessment tool pain has been explored as a way of improving how parents manage their child. However, the use of a pain assessment instrument had no significant impact on the doses of administered analgesics (Unsworth et al., 2007). Several other factors, such as a child's biopsychosocial background and parental concerns have been shown to influence a child´s pain and the influence of these factors on pain assessment will be reviewed in the next section.

2.10.1. Barriers in pain assessment

The biopsychosocial model of pain is the framework of understanding the complexity of paediatric pain (Gatchel et al., 2007). A child's pain experience depends on those people around the child and who perceives this pain (e.g., caregiver). The child expresses pain, the receiver decodes the signal as pain (rather than other emotions or sensations) and reacts to it (Finley et al., 2009). Facing a child in pain generates numerous responses in observers that may impact caregiving, and hence the child's pain. These responses can be other-oriented feelings such as emotional sharing or self-oriented feelings of personal distress. Both feelings can be important determinants of an intention to intervene (Lin & McFatter, 2012). Among these interventions, estimations of pain and decisions regarding provision of pain relief are central for pain alleviation.

Even when the caregiver evaluates pain correctly, this may not lead to effective pain relief because treatment is influenced by institutional and social factors, and parents or clinicians may fear the administration of analgesics or the need to relieve pain (Fortier et al., 2012). Caregivers' expectations and interpretations are influenced by their cultural and social backgrounds, beliefs and experiences as well as the culture of the institution where they work, which all form the caregivers' response to a child's pain (Finley et al., 2009). For example, in a study by Forgeron, Finley, & Arnaut (2006), parents indicated that it was the child´s responsibility to express pain: "to cry a lot" or "complain" or "talk about pain". No parent suggested that the child should be asked about their pain, meaning that no self-reporting was elicited. Nurses in turn, expected that it was their responsibility to identify pain by behavioural signs, not by asking the child. Ideally, the child should be asked and provide self-reports whenever possible. Caregivers should acknowledge a child's self-reports and react to provide effective pain relief (Linder & Wawrzynski, 2018). However, several studies found differences between the HCPs' perception of a child's pain and the parents' or child's perception of that pain. For example, Miser, Dothage, Wesley, &Miser (1987) identified discrepancies regarding cancer pain severity when comparing child versus investigator pain assessments with children reporting higher levels of pain. During the cancer treatment pathway, parents increasingly thought they were better judges of their child´s pain than nurses and doctors (Ljungman et al., 2000). HCPs believed that they controlled pain while the children and their parents perceived otherwise (Van Cleve et al., 2011; Zhukovsky et al., 2015). In contrast, when behavioural manifestations were absent, only 49% of paediatric nurses believed a child´s pain report (Van Hulle Vincent & Denyes, 2004). Ultimately, correct pain assessment is required to provide sufficient pain relief, as underestimation of pain is often associated with undertreatment of pain (Twycross, Parker, et al., 2015).

Even though self-reporting is generally recommended for symptom estimation, there may be advantages in investigating different perspectives in pain perception. Thus, a study of the factors that were associated with child, parent, and nurse ratings of acute paediatric pain and distress during venous puncture showed that nurses' ratings were based upon overt distress, parents' ratings reflected their subjective perception of the child's pain, and the child's self-report was associated with the child's chronologic age (Manne et al., 1992). One advantage of investigating a child´s pain from a parental perspective as opposed to a child's perspective, is that reports for every child will potentially be provided (including those who cannot respond for themselves). Moreover, the use of the same instrument regardless of the child´s age may facilitate data collection in rare conditions

(Hedén et al., 2013). However, using different informants involved in child´s care, such as parents, nurses or doctors, may identify different aspects of pain in a child. This is in line with the new trends in the definition of pain, which suggests that pain is more than a single individual's experience as it integrates the subjectivity of the persons involved in pain evaluation and management (Cohen et al., 2018). Despite the key pain care roles of parents and HCPs, there is limited knowledge in the area of pain perception in HCPs versus parents, as these differences in perception may impede better pain control.

In this section, methods of pain assessment and barriers to their use have been reviewed. A child's pain may be perceived differently by the child, the parents and the clinicians and may result in feelings of distress among parents and HCPs. The challenges experienced in pain management will be presented in the next section.

2.11. Challenges in pain management

2.11.1. Parental attitudes toward pain and pain medication

Parental perception of disease and pain influence and interact with the ways in which parents approach their child's pain assessment and management (Finley et al., 2009). Parental concerns and misconceptions regarding analgesic use for children have been associated with less administration of analgesic doses or use of less potent analgesics then recommended (Rony et al., 2010). Moreover, parents hold misconceptions about how children express pain, including the belief that children always verbalize their pain or that their pain is not severe enough to administer medication. Parents who endorse more favourable attitudes regarding analgesic use for children are more likely to administer analgesia (Fortier et al., 2014).

Parents are frequently reluctant to provide adequate analgesia in infants and very young children, a tendency that may reflect the belief that pain medication is dangerous (Pillai Riddell et al., 2008). Moreover, parents believe that it is best to avoid pain medication because they are concerned about addiction and the side effects of analgesia (Rony et al., 2010). The most feared side effects are respiratory depression and over-sedation; both patients and caregivers commonly believe that they must choose between a child being either in pain or being over sedated (Friedrichsdorf, 2017). However, serious clinical incidents due to opioids administration are infrequent. In a national audit of paediatric opioid infusions across the UK, only 0.13% of patients experienced respiratory

depression. Ten of the fourteen children had associated morbidities (cerebral palsy, cardiac or haematological disease) and were therefore more sensitive to opioids (Morton & Errera, 2010).

In addition to these concerns, parents may view cancer pain as a referent for disease status leading to pain taking on an existential meaning. A prescription of morphine then becomes a metaphor for impending death (Flemming, 2010). Parental understanding of pain and pain medication develops throughout a child´s disease and is related to HCPs᾽capacity to educate and support families (Bettle et al., 2018). This in turn depends on HCPs᾽knowledge of pain as well as their perception of a child's pain and anxiety and parental distress (Hedström et al., 2006). The literature reveals a need for further understanding of parental beliefs about pain medication in ALL and how these are perceived and addressed by HCPs.

2.11.2. Pharmacological pain management

An increased awareness of improving pain relief has resulted in guidelines for the management of cancer-related pain in children built up as a three step analgesic ladder developed by the World Health Organisation (WHO) (McGrath, 1996). Based on this ladder, national paediatric societies have developed local guidelines for pain management. Step-1 includes basic analgesics such as paracetamol, Step-2 includes weak opioids such as tramadol, while Step-3 includes opioids (morphine, fentanyl, oxycodone or methadone). Opioids are recognized by the WHO as essential for treatment of moderate-to-severe pain in children and are the mainstay of oncology pain management (Getz et al., 2018). Adjuvant analgesia (e.g., gabapentin and tricyclic antidepressants) may either be indicated to achieve an opioid-sparing and/or managing a neuropathic or visceral pain component. Analgesic treatment should be individualized according to the child's pain, age, weight, condition and his/her response to treatment. Some children may need high doses of opioids to control severe cancer pain and treatment effectiveness should be frequently assessed, reassessed and modified as required (Friedrichsdorf, 2017).

WHO guidelines seem to provide efficient pain control in childhood leukaemia. A study of 61 patients documented that most children could be treated according to WHO guidelines. Of the 39 children, who needed referral to pain and palliative care services, only six (15%) children required opioids (Geeta et al., 2010).

Getz et al found that 77.7% of children with leukaemia were exposed to opioids. This exposure was highest during the first treatment phases reflecting higher patient acuity at diagnosis and greater treatment-related complications in those phases (Getz et al., 2018). This explanation was supported by the parallel increase in Paediatric Intensive Care Unit (PICU) utilisation. Furthermore, the opioid utilisation increased with age but did not differ by gender, race or insurance status.

In these vulnerable patients with a complex pain situation, analgesics alone are often insufficient. Depending on the child's condition, nonpharmacological pain relief modalities like physical therapy and exercise, distraction, family and peer support, hypnosis, returning to school and normalizing social life are usually the most effective ways to reduce pain and normalize functions (Friedrichsdorf, 2017). Non-pharmacological pain relief will be further highlighted in the next section.

2.11.3 Non-pharmacological pain management

Research on non-pharmacological pain relief in children has been mainly conducted in postoperative settings (He et al., 2010; Sng et al., 2013). Studies showed that nurses used imagery, positive reinforcement, thermal regulation, massage positioning and distraction. Although these studies provided evidence for HCPs to consider more pain relief, nurses reported that education alone was not sufficient to optimise nurses' use of these methods, as various barriers limited their practice, such as workload/lack of time and the child's inability to cooperate (He et al., 2010).

At home, the most frequently used nonpharmacological pain alleviation methods in children aged one to six years old included familiar strategies from everyday life, like holding the child on the parent's lap, comforting the child and spending more time with them. Differences were found in mothers' and fathers' use of these methods and several methods were used more with girls than with boys. Significant relationships were found between parents' use of non-pharmacological pain relief methods and children's pain intensity and pain behaviour (Kankkunen et al., 2003).

In children with cancer, non-pharmacological pain relief methods were only used in a limited number of cases (26%) (Plummer et al., 2017). Research indicates that hypnosis was the only method that resulted in statistically significant reductions in anxiety and pain, while evidence from non-hypnosis interventions was equivocal (Nunns et al., 2018). However, parents used more non-

pharmacological strategies to manage a child's pain than pain medication. Among these strategies, distraction was the most common method used by parents (Tutelman et al., 2018).

Studies on paediatric pain management add valuable information about the use of analgesic medication and various non-pharmacological pain relief methods but they also reflect the challenges met by clinical research: paediatric oncology populations are small and in homogeneous, study designs, settings and outcomes may differ and comparisons between treatments are difficult (Mercadante & Giarratano, 2014; Twycross, Forgeron, et al., 2015).

2.12. Summary

There is clear evidence that pain is a common and serious symptom experienced by children with ALL. Pain in leukaemia can be controlled by pharmacological and non-pharmacological strategies, but barriers may lead to suboptimal treatment. Unrelieved pain can negatively affect quality of life, result in patient and family distress and is associated with long-term morbidity. Child and parent anxiety and distress impact on a child's experience of pain and how this pain is perceived by parents and HCPs.

2.13. Areas that need further work

This chapter reveals that there is a need for further research regarding the experience of parents and HCPs with a child's pain in ALL. Research on parental response to a child's pain indicates that parental anxiety may play an important role in it and the functioning of the child during cancer treatment. Limited evidence exists describing how clinicians perceive the distress of children and parents and how this influences decision making in pain alleviation. Because of the subjective nature of pain, exploring beliefs, meanings and perspectives of parents and HCPs may contribute to a better understanding of pain in the context of ALL.

There is a lack of research concerning self-reported pain data provided daily by parents or older children throughout the first months of ALL treatment, which are the most stressful. Previous longitudinal studies of pain in children with leukaemia have collected data at few time points during the study period. Digital technologies can be used to collect real-time data and provide a more nuanced picture of the patients' diseases and reactions to treatment. In addition, this approach illustrates the challenges met by the patients involved in electronic self-monitoring of symptoms. Using the perspectives of different informants involved in a child's care, such as parents, nurses and

doctors as well as child's self-reports of pain may identify different aspects of pain experience in childhood ALL. Furthermore, these self-reports of pain may support the interpretation of parents' and clinicians' perspectives on a child's pain. Thus, there is a need for further research that emphasises the interactions between the child, parents and clinicians in relation to pain.

2.14. Research question

The overarching research question leading from this literature search is:

"How is pain associated with childhood ALL experienced, understood and managed by children, parents and clinicians?

2.15. Aim

The aim of this thesis is to investigate the experience of pain and its management during ALL from the perspective of the child, parents and clinicians.

2.16. Objectives

There are three overarching objectives of this thesis:

1. To explore the experience of parents and clinicians in pain assessment and management in childhood ALL.
2. To examine pain characteristics and the use of pain relief strategies in self-reported data in childhood ALL.
3. To evaluate the use of electronic data on child´s pain assessment and management reported by children or their parents during a three-months period of ALL treatment.

3. Chapter 3 Methodology

3.1. Overview of Chapter 3

This chapter outlines the methodology used in this doctoral research. The first section presents an overview of the mixed methods approach and why it has been chosen. The next section describes the ontological and epistemological considerations that underpin the qualitative and quantitative methodology. This is followed by a presentation of the qualitative and quantitative research methods and their roles in the current research. This chapter continues with a description of how the findings from the two studies will be mixed with reference to theories on the design of mixed methods studies. The final sections present the two studies conducted as part of this research.

3.2. Mixed methods research

The literature review presented in Chapter 2 identified that children with ALL and their parents reported pain as one of the most problematic symptoms during the disease pathway. Pain is by definition a personal experience (IASP, 2020) and a child's pain experience integrates the subjectivity of both child and caregivers (Cohen et al., 2018). Thus, understanding pain in childhood ALL requires a detailed knowledge about the experience of pain and its management from the perspective of the child, parents and clinicians. Different research strategies may be needed to achieve this knowledge and both qualitative and quantitative strategies are recognised as a valuable means of investigation within pain research (Morse, 2015). The terms qualitative and quantitative research refer to both the techniques of data collection and analysis and to the wider frameworks for conducting research, qualitative and quantitative paradigms, which will be described later in this chapter (Braun & Clarke, 2013d).

Children's pain experience can be examined using a quantitative approach to obtain data on pain characteristics and management. Quantitative research emphasises quantification in the collection and analyses of data (Bryman, 2012c). For example, rating pain intensity numerically on a pain scale facilitates the quantification of a subjective experience. Data can be analysed using statistical methods that may allow generalisation for a larger population. However, quantitative research can be limited by its focus on statistical relationships and cannot provide a subjective understanding of individual interactions and interpretations of pain (Morse, 2015). Qualitative research can enhance knowledge about a complex phenomenon such as pain focusing on words and language as data and

various methods to analyse these data (Bryman, 2012b). Using qualitative research to explore the experience of parents and HCPs with pain assessment and management in ALL may provide understanding of different views, attitudes and beliefs that are difficult to access through other methods (Morse, 2015). Moreover, a qualitative approach may provide understanding of the subjectivity involved in the process of decision-making regarding pain alleviation. However, a qualitative approach cannot objectively measure the intensity of pain or the exposure to pain medication. Therefore, neither quantitative nor qualitative findings alone could adequately answer the research question.

Using a mixed methods approach that combines qualitative and quantitative research in the same project is a relatively new strategy, having only gained popularity during the last 20-30 years (Bryman, 2012a). Supporters of this approach emphasise that it allows researchers to use the strengths of both quantitative and qualitative approaches while avoiding the drawbacks of each (Johnson & Onwuegbuzie, 2004). Furthermore, this type of research offers advantages compared to monomethod research because it presents a supplementary perspective, that is not just the quantitative or qualitative but both (Bergman, 2011).

A mixed methods approach was chosen for this doctoral research for several reasons. Firstly, to provide depth of understanding in relation to the research question. Secondly, to provide the framework for data interpretation (Johnson & Onwuegbuzie, 2004). Triangulation of data was used to compare/contrast findings on the same topic, which were collected using different methods and at different time points. The interpretation of the quantitative results generated support for the understanding of parents' and HCPs attitudes and beliefs about a child's pain assessment and management in ALL. In addition, the interpretation of the qualitative findings was used to enhance the understanding of a child's quantitative pain reports. The interpretation of data in mixed methods research brings the researcher into the centre of research activities and allows the researcher to contribute differently, providing a more critical or personal interpretation, compared to researchers engaged in monomethod approaches (Bryman, 2012a). Therefore, adopting a mixed method approach in this thesis aims to provide a novel understanding of pain experience in childhood ALL.

3.3. Philosophical position

In research practice, researchers rely on philosophical assumptions made about ontology and epistemology. Ontology is the study of what there is in the world and determines what we think about reality. Thus, reality can be seen entirely independent of human understanding (realism) or dependent on human interpretation and knowledge (relativism) (Bryman, 2012b). Realism assumes that there is only one reality and the truth can be accessed through scientific methods. In contrast, relativism argues that there are multiple constructed realities. What is "true" and "real" is dynamic across time and context and accordingly, perspectives and reality are shaped by individuals (Braun & Clarke, 2013d). Realism is the ontology underpinning most quantitative research while relativism underpins some qualitative approaches (Braun & Clarke, 2013d).

Epistemology is the study of knowledge and how to understand it. Epistemology also determines what is trustworthy knowledge and different epistemological approaches imply different ways of "knowing" the world (Scotland, 2012). Researchers may refer to an epistemological position of for example, positivism, critical realism or interpretivism (Reeves et al., 2008). Positivist philosophy assumes that the reality is stable and phenomena (e.g., diseases, humans or institutions) exist whether we are looking at them or not and whether we understand them or not. Thus, human understanding may be flawed, but there is a potential 'right' explanation (Green & Thorogood, 2014b). Critical realism is based on real world phenomena and linked with societal ideology. Knowledge is both socially constructed and influenced by power relations from within society. Critical realists focus on generating mechanisms that can transform status quo (Haigh et al., 2019; Scotland, 2012). The interpretivist philosophy adopts the view that the researcher understands and interprets individual behaviour and respects that people are different as well as the objects of natural science (Green & Thorogood, 2014b). Therefore, in order to understand the social world that is created by its social actors, one must understand the subjectivity of social actions and how this constitutes and creates our social world (Bryman, 2012b).

Whilst a range of epistemological approaches exist, interpretivist and positivist paradigms are most strongly associated with qualitative and quantitative research, respectively. A relativist interpretivist position accepts that there are various realities that contribute to the process of knowledge as opposed to the realist positivist position (Green & Thorogood, 2014b). Adopting a relativist interpretivist position for the qualitative research in this thesis, the researcher sought to gain understanding of parents' and HCPs' experiences with the assessment and management of a child´s pain in ALL. This position assumes that the experience of pain is created through interactions of

individuals and is subject to endless change as new interpretations of this phenomenon happen. Additionally, this position can generate knowledge about a child´s pain through exploring the meanings of parents and HCPs created within a context.

The two philosophical assumptions of realism and positivism are the basis for a scientific research paradigm in which the truth (e.g. pain) is assumed to be value-free, separate from emotional, subjective or political viewpoints and simply observed by the researcher (Braun & Clarke, 2013d). In this thesis, the quantitative research adheres to objective ontology with a positivist epistemological approach that governs the basis for the conventional and traditional scientific methodology, involving statistics and generalisations.

Thus, ontological and epistemological assumptions were incorporated into the ways in which research was carried out and this will be elaborated upon in the next section.

3.4. Methodological approach

In relation to methodological issues, it is helpful to distinguish between qualitative and quantitative research. In this section, paradigms associated with qualitative and quantitative types of research are described and their opportunities and limitations are acknowledged.

3.4.1. Qualitative research

Qualitative research is an approach to the study of the social world, which seeks to describe and analyse the culture and behaviour of humans from the point of view of those being studied. Qualitative research tends to emphasise an inductive approach to the relationship between theory and research (Bryman, 2012b). Data collection methods are less fixed and more closely related to "real-life", (e.g. interviews) consistent with the idea of making sense of data in context (Braun & Clarke, 2013d). Furthermore, the recognition that researchers bring their subjectivity (views, perspectives and beliefs) into the research process is seen as a strength rather than a weakness (Braun & Clarke, 2013d).

In qualitative research, quality criteria refer to credibility (confidence in the truth of the findings), transferability (the extent to which the findings can be transferred or applied in different settings), dependability (the extent to which the findings are consistent in relation to the contexts in which

they were generated) and confirmability (the findings are based on the study's participants and settings instead of researchers' biases) (Braun & Clarke, 2013c).

In relation to research findings, a distinction is made between quantitative and qualitative methodologies in terms of nomothetic and ideographic modes of reasoning. Quantitative research usually takes a nomothetic approach, seeking to establish findings, which can be held irrespective of time and place. In contrast, qualitative research usually takes an idiographic approach, which locates its findings in specific time-periods and locales (Shareia, 2016). Thus, understanding reality from the participant´s perspective may be better achieved through ideographic methods, which focus on the individual and emphasise the unique personal experience of human nature (Shareia, 2016).

Qualitative research in this thesis

A basic way of characterising qualitative studies is to describe their aims as seeking answers to questions about why, what or how of a particular phenomenon (Braun & Clarke, 2013d). In this thesis, the role of the qualitative approach is to answer how pain associated with childhood ALL is experienced and understood by parents and clinicians. Qualitative research can give voice to parents' and HCPs' own meanings, perspectives, beliefs and experiences with a child's pain. Furthermore, it can provide in-depth, rich and detailed data, where multiple truths are accepted (Bryman, 2012b). Parents have a pivotal role in caring for their children throughout the ALL therapies and their capacity for parenting can help the child cope with the illness (Tremolada et al., 2005). Moreover, a parent's perception of his or her child's symptom severity is an important determinant of symptom severity assessment and health care interventions (Dupuis et al., 2016). However, parents play different roles to health professionals, and differ in their knowledge, skills and experiences. Nurses have more technical medical knowledge and would be expected to be more skilled in pain assessment than parents (Bettle et al., 2018). Doctors possess highly specialised medical knowledge and are likely to see a greater number of different cases than nurses but spend less time with individual children in their care (Levine et al., 2019). Thus, in ALL, given the magnitude and variation of these experiences that form the assessment and management of a child's pain, the researcher chose to explore the perspectives of parents, nurses and doctors. Understanding the perspectives of parents and clinicians with different professional backgrounds is an essential tool to identifying ways to provide effective pain relief.

3.4.2. Quantitative research

Quantitative research allows us to acquire knowledge about the objective reality. Using a deductive approach to the relationship between theory and research, this type of research generally seeks to answer questions about “how much” or “how many” (Bryman, 2012c). Furthermore, this type of research seeks to identify relationships between variables, to explain or predict as well as to achieve consensus, norms or general patterns (Braun & Clarke, 2013d).

Quantitative researchers tend to adopt a static view that exists independently of the researcher (Shareia, 2016). These researchers value objectivity that refers to the extent to which personal biases are removed and value-free information is gathered (Bryman, 2012c). Furthermore, validity, which is used to measure what it is intended to measure, is highlighted as an important quality criterion for quantitative research, referring to both internal validity (the research has proven or disproven the hypothesis) and external validity or generalisability (Braun & Clarke, 2013c). In addition, other important aspects of quantitative research are reliability and consistency (Braun & Clarke, 2013c).

Theories are the starting point for investigations within quantitative research and research methods tend to be structured, in the sense that sampling determination and data collection instruments are designed before a data collection process (Shareia, 2016). Quantitative data collection may include various methods that will generally result in numerical values: 1) Experiments and clinical trials 2) Surveys, interviews and questionnaires that collect numerical information or count data by using closed-ended questions 3) Observing or recording well-defined events, such as the number of procedures and 4) Obtaining information from a Management Information System. Data can be analysed using statistical methods that may allow generalisations to a larger population (Braun & Clarke, 2013d).

Quantitative research in this thesis

Quantitative research is frequently used to determine the prevalence and intensity of pain in different populations. Previous longitudinal studies of pain in children with leukaemia collected quantitative data at only 3-7 time points during the study period (the first year after diagnosis) and reported that pain was one of the most problematic symptoms (Dupuis et al., 2016; Van Cleve et al., 2004). In this thesis, the researcher adopted a quantitative approach to examine the child’s pain

experience through daily self-reported data on pain during the first three months of ALL treatment. Quantitative data on pain characteristics and the use of pain relief strategies reported by the child or parent (of children younger than 10 years old) aimed to provide a picture of pain and pain management strategies experienced by patients with ALL.

3.4.3. Opportunities and limitations of qualitative and quantitative research

Over the last few hundred years many sciences have focused on "realist" assumptions grounded in experiments and observations of the natural world. Quantitative research has been considered the traditional way to provide objective, rational and neutral scientific evidence. (Green & Thorogood, 2014b). In contrast, qualitative work based on subjectivity has not always been regarded as "scientific" (Green & Thorogood, 2014b). Knowledge emerging from qualitative research is highly subjective and contextualised and generally ranks as low in the hierarchy of evidence (Fitzpatrick & Boulton, 1994). Validity is often highlighted as a limitation of qualitative research (Baxter & Jack, 2008). However, qualitative researchers emphasise that subjectivity and context allow the researchers to answer questions that cannot be answered from a quantitative perspective. Thus, attempts to conceptualise qualitative research according to quantitative principles (e.g. generalisability as a result of statistics) do not improve the quality of research (Bryman, 2012b). Qualitative research has the potential to provide evidence for people´s views and beliefs, about what people know and how they act. In health sciences, qualitative research is valuable to answer questions about understandings of human health, health behaviour and health services (Green & Thorogood, 2014b).

The large focus on subjectivity and context in the qualitative research were the reasons why the researcher wanted to examine quantitatively the truth that lies out there, such as "how much" pain (e.g., pain intensity and frequency) children report daily during the first period of treatment in childhood ALL. Therefore, the researcher adopted the ontological position of one reality, that of whether children with ALL experience pain or not. This view is in line with what is expected from a positivist (realist), where the researcher aims to acquire knowledge about the objective reality (Bryman, 2012c). However, objectivity in quantitative research is influenced by judgements and decisions (such as selection of variables) made during the process of research (Johnson & Onwuegbuzie, 2004). This type of research also has the problem that when statistics are generalised, the intentionality and subjectivity of the participant is completely ignored (Scotland, 2012).

3.4.4. Combining methods in a mixed methods study

Limitations exist with both qualitative and quantitative research approaches. Some limitations could be counteracted by using both methodologies and adopting a third paradigm, “mixed methods.” A mixed methods approach is not just a combination of the other two paradigms; it is established alongside the other paradigms with its own philosophical underpinning. All three, quantitative, qualitative, and mixed methods paradigms thrive and coexist in the research world (Johnson & Onwuegbuzie, 2004).

There are various views on how quantitative and qualitative positions should be used within the same project. Some researchers consider the philosophical standpoints of these two methodologies to be incompatible, resulting in their parallel use with each maintaining their strengths while others have combined their use as a result of their efforts to highlight the similarities between the two (Zhang & Creswell, 2013). “Mixing” qualitative and quantitative approaches can be performed across the stages or there can be separate qualitative and quantitative phases, which are carried out sequentially or concurrently and then the findings are integrated (Johnson & Onwuegbuzie, 2004). Furthermore, these approaches can be equal, or one may be dominant. There are several variants of mixed methods design, such as triangulation, embedded design, explanatory design and the exploratory design (Creswell, 2006). "Mixing" in mixed methods is more than just the combination of two independent components of the quantitative and qualitative data. Three main "mixing" procedures have been described: 1) the researchers analyse the two types of data at the same time but separately and integrate the results during interpretation; 2) the researchers connect the qualitative and quantitative portions in phases in such a way that one approach is built upon the findings of the other approach; and 3) the researchers mix the two data types by embedding the analysis of one data type within the other (Zhang & Creswell, 2013).

Mixed methods in this thesis

A mixed methods approach was chosen to understand the experience of pain and its management during ALL from the perspectives of child, parents and clinicians. The type of “mixing” used in this doctoral research follows one of the “mixing” procedures described by Zhang and Creswell (2013): the researcher analyses the two types of data at the same time but separately and integrates the results during interpretation.

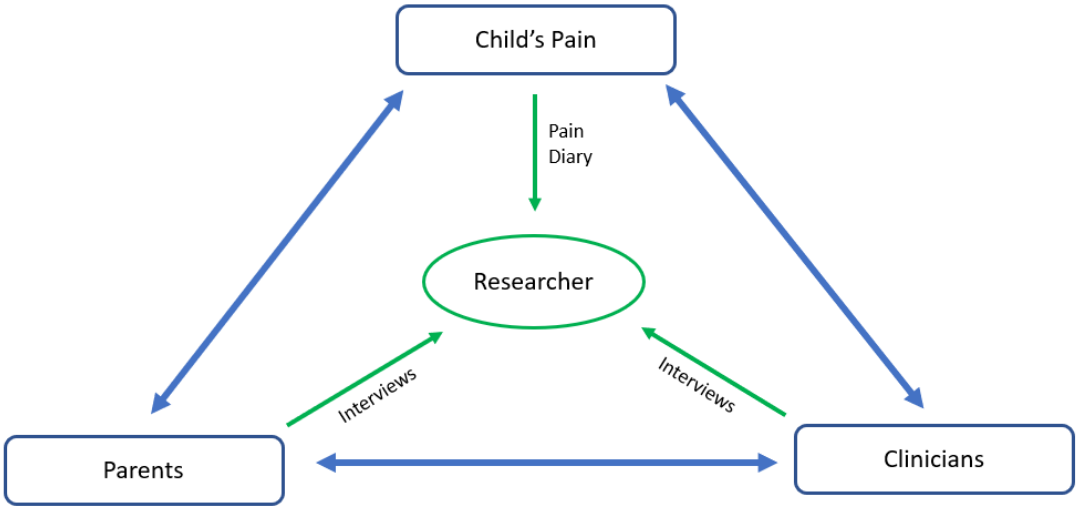
A longitudinal design was adopted in the quantitative study (reported in Chapter 6) to describe the reality that may exist regarding the prevalence and characteristics of pain, activity and mood as well as the use of pain relief methods to address the problem in a population of children with ALL. However, these quantitative data needed to be placed in the context of understanding the parents´ and HCPs' experiences with a child´s pain as well as their perceptions, attitudes and beliefs about this phenomenon. Therefore, semi-structured interviews were carried out with parents of children with ALL and HCPs involved in the care of those children (reported in Chapter 4). Different samples of participants were used to collect these two data sets to avoid extensive parental burden associated with participation in two research studies (Molinaro & Fletcher, 2018). The qualitative and quantitative findings were triangulated in Chapter 8. Here the evidence is discussed in relation to the extent to which the results of each study support or conflict with the findings of the other study or explains unexpected findings.

Triangulating the data

Triangulation was used to secure the understanding and the depth of research (Denzin, 2012). The notion of triangulation borrows a metaphor from navigation and refers to a measurement technique often used to locate an object in space by relying on two known points in order to ‘‘triangulate’’ on an unknown fixed point in that same space (Mertens & Hesse-Biber, 2012). Thus, depending on the angle at which the researcher looks at these points, different points and configurations are revealed to the viewer (Denzin, 2012). Triangulation occurred between the researcher's view, parent/HCPs perspectives and the child´s report, as illustrated in Figure 3.1.

Figure 3.1.

Overview of triangulation process



In this figure, the two-way arrows illustrate potential pathways between the child, parents and clinicians in relation to pain experience. The researcher sought to connect parents' and HCPs' perspectives collected in interviews with the child's (or parents') reports from pain diaries.

The priority in the triangulation process and data interpretation was the qualitative research. Data from pain diaries supported the qualitative findings such as the investigation of pain intensity and frequency and the use of pain relief methods. Additionally, quantitative data supported the explanation of challenges associated with pain research in ALL (e.g., missing data due to fever, surgery or even death). Using a mixed methods approach allowed the researcher to play an active role and choose within and between a multitude of qualitative and quantitative components (Bergman, 2011). The unique result of the choices and interpretation in this research add data and novel perspectives to the literature regarding pain in childhood ALL.

To fulfil the aim and objectives for this doctoral research outlined at the end of Chapter 2, two studies were conducted using a qualitative and a quantitative approach, respectively. The results of these studies were integrated using the mixed methods approach described above. Considerations regarding the research design, research setting and sample as well as data collection methods and data analysis used in these two studies are described below with in-depth detail provided in Chapters 4 and 6.

3.5. Research design

Research design refers to the logic of the study; specifically, to what, how and why of data production. This includes the type of study (e.g. experiments or case studies) and the methods of data production (Green & Thorogood, 2014b). Some researchers select experiments to demonstrate cause and effect relationships and to evaluate interventions (e.g. employing comparisons between experimental and control groups with regard to the dependent variable) (Bryman, 2012b). Case studies are the research design of choice when a how or why question is being asked about a phenomenon (Green & Thorogood, 2014b). According to Flyvbjerg, a case study is a strong design format for addressing questions, which require detailed description and an essential design for developing an understanding of health, illness and healthcare in context (Flyvbjerg, 2006). Some case studies are cross-sectional (research on a sample at a single point in time) whilst others are longitudinal (research on a sample on more than one occasion). Furthermore, adopting a case study as a research design permits the investigation of a small number of naturally occurring cases as opposed to surveys or experiments in which a large number of cases are investigated (Bryman, 2012c). From a positivist perspective, single case studies are often seen as a design with a relative limited scope for generalising. However, a case study design is preferable when depth and accuracy are needed.

Study 1 adopted a qualitative cross-sectional approach to investigate the experience of parents and clinicians in association with a child's experience of pain. This approach was utilised to ensure a deep engagement with the underlying mechanism that constructs this specific phenomenon (a child's pain) within its context (e.g., hospital ward) and to facilitate the collection of rich in-depth data in this field.

Study 2 adopted a case study design to explore pain in childhood ALL. Leukaemia is a low-prevalent condition, which is experienced differently depending on different factors, such as response to chemotherapy and the developmental stage of the child. Therefore, it seems relevant to adopt a descriptive approach that can describe the phenomenon (child's pain) within its context (e.g., disease pathway). In addition, adopting a developmental, longitudinal design allowed the researcher to explore how pain changed over time in a group of children with ALL.

In this doctoral research, the study design and approach to data analysis were based on a biopsychosocial framework of paediatric pain. Specifically, the integrative conceptual model focused on the individual parenting variables and the dyadic interactions with the child. This model

also emphasises the developmental context of the complex and bidirectional child-parent relationship and the dynamic, progressive nature of changes in relationships (Palermo & Chambers, 2005). The fear-avoidance model informed the understanding of the psychological responses to pain and pain management behaviours (Asmundson et al., 2012). Furthermore, as children with ALL rely on their parents, HCPs and other adults for caregiving, the social communication of pain model emphasised the social context of pain expression for the assessment and alleviation of this pain (Craig, 2009). In addition, the assumptions and choices made in this research included the researcher's personal experience. As a paediatric anaesthetist at a tertiary hospital, the researcher has treated children with ALL who were in pain and has often reflected on the parents' and HCPs' roles in the assessment and management of paediatric pain. Berger (2015) argues that there are both benefits and challenges when the researcher has some familiarity with what is being studied. Moreover, the author emphasises the role of reflexivity in the transformation of researcher's subjectivity into a positive tool in research (section 4.3.1.).

3.6. Research setting and sample

This doctoral research is performed in Denmark, where children with ALL are treated at four tertiary hospitals (Copenhagen, Aarhus, Odense and Aalborg). Participants were recruited from the paediatric oncology department at Aarhus University Hospital, where the researcher is an anaesthetist.

3.6.1. Sampling methods

Research involves the selection of a data sample, meaning that issues of sampling methods, sample size and recruitment strategies need to be adressed (Robinson, 2014). Researchers commonly examine traits or characteristics of populations in their studies. In most cases, it is impossible for researchers to collect information from all existing cases, therefore, through the process of sampling, researchers select individuals with some commonality. Researchers aim to find a representative sample of the population and the results of the study can be generalised and applied to the overall population. The group of individuals who have the legitimate chance of being selected are referred to as the sampling frame. There are two main types of sampling: probability and non-probability sampling (Wu Suen et al., 2014)**.** The difference between the two types is whether the sampling selection involves randomization, which occurs when all members of the sampling frame have an equal opportunity of being selected for the study. Using a random selection, researchers

seek to generate a representative sample of the population from which it was selected. When a representative sample is used, the results are more likely to accurately reflect the entire population (Bryman, 2012c).

Non-probability sampling is typically employed in studies where randomization is not possible in order to obtain a representative sample (Wu Suen et al., 2014). Non-probability population sampling method is useful for pilot studies, case studies, qualitative research, and for hypothesis development. Bias is more of a concern with this type of sampling. Non-probability sampling includes purposive, convenience, consecutive, judgmental, quota and snowball sampling.

In Study 1, purposive sampling was chosen to make the most of the available resources by obtaining the greatest depth and breadth of information from a few participants (Braun & Clarke, 2013d). This approach involved the identification and selection of a representative sample of participants who were well-informed with the phenomenon of interest and who were able to assist with the relevant research (Wu Suen et al., 2014).

In Study 2, consecutive sampling sought to include all available individuals who agreed to participate, provided they met pre-established criteria (Wu Suen et al., 2014). This sampling approach can be considered the best choice for non-probability sampling techniques since by studying everybody available, a good representation of the overall population is possible in a reasonable period of time without incurring the cost or time required to select a random sample (Setia, 2016). Consecutive sampling can be useful when the available subject pool is limited or when using selection criteria so stringent as to reduce the number of subjects to a point that threatens the generality of findings. Although consecutive sampling methods are typically stronger than other non-probability methods in controlling sampling bias, such differing influences cannot be ruled out. Response rate and the proportion of the subjects willing to participate of those selected, may also influence the validity of inferences. For instance, participants who agree to participate may have different motivations or life circumstances than those who do not (Setia, 2016).

3.6.2. Sample size

The calculation of sample size is affected by numerous factors, including the nature of the topic, study design and methods (Sandelowski, 1995). Another important consideration regarding sample size is to ensure enough richness and adequacy of data (Vasileiou et al., 2018), but not so much data

that it precludes complex engagement with the data in the time available (Onwuegbuzie & Leech, 2007). When describing the characteristics of a group, for example pain intensity, the larger the study the more reliable the results. Furthermore, when comparing characteristics between two groups of participants (e.g. pain in small versus older children) the size of the study depends on the magnitude of the target parameter (Hackshaw, 2008). However, the number of children with ALL is limited. A study based on many participants would take several years and large resources to complete. A small study can address the research question in a relatively short time and can be conducted in one or few centres. Furthermore, the results from a small study can be useful in clinical practice and when designing larger studies (Hackshaw, 2008).

3.7. Data collection methods

In Study 1, data was obtained through semi-structured interviews, the dominant method of collecting data for qualitative interviews (Braun & Clarke, 2013b). The interview method facilitates gathering rich and in-depth data in a flexible way, which is needed to understand the phenomenon. In semi-structured interviews the focus is on the participants' subjective perspective, which is facilitated by open-ended questions. The researcher has a list of questions and the participants are given the opportunity to raise issues that were not anticipated by the researcher. In contrast, a structured interview would include predetermined response categories, while an unstructured interview would be strongly participant-led (Fitzpatrick & Boulton, 1994). However, as the study had a defined topic of interest from the beginning, a semi-structured interview guide was used to support the participants to express their own perspectives regarding the child's pain experience.

In Study 2, the researcher sought to obtain knowledge about pain from children with ALL (and parents of children younger than 10 years), who were asked to complete pain diaries during the first three months of treatment. These pain diaries completed via a mobile application (phone, tablet or laptop) were used daily to collect data on pain intensity, frequency, location, the impact of pain on a child's life (activity and mood) and the use of pain relief strategies. These pain characteristics were rated numerically on simple scales to facilitate the quantification of a subjective experience (Tomlinson et al., 2010).

3.8. Data analysis

Study 1 utilised an inductive approach to analyse data collected through interviews with clinicians and parents of children with ALL. Inductive reasoning includes specific observations as well as broader generalisations and theories, whereas in contrast, deduction moves from the general to the specific. Therefore, the inductive approach is most often used in interpretative research (Green & Thorogood, 2014a). Several types of qualitative analysis were considered. Content analysis may have led to a loss of complexity and meaning provided by study data and would not have provided the depth that this analysis aimed to achieve (Bryman, 2012b). Framework analysis was not chosen as it is more geared towards generating practice and policy-oriented findings, involving summarising and classifying data within a thematic framework (Green & Thorogood, 2014a) . Due to its flexibility and applicability across a range of theoretical frameworks, thematic analysis was considered the appropriate analytic approach. Thematic analysis involves searching data for repeated patterns and understanding how these patterns fit within a data set to tell a story (Braun & Clarke, 2013a). Braun & Clarke (2019) have further described their method as "reflexive thematic analysis". In this type of analysis, themes are conceptualised as analytical outputs created from codes through the researcher´s active engagement with their data. The reflexive approach emphasises the interactive process between data, the researcher and the context of the research itself.

In Study 2 data collected in the mobile application was exported to Excel and analysed using the statistical software package STATA 13. Descriptive statistics were used to describe the mean features of data separately on every participant (frequencies and percentages, means and standard deviation, medians and quartiles). Based on the sample of participants in the study, data was sliced up and the Mann-Whitney U test was used to compare the burden of pain in two different age populations (e.g., pain intensity in children younger than 10 years compared to children older than 10 and teenagers). This test captures the entire distribution for the two populations that may be not normally distributed, for instance due to different number of participants and pain reports. The criterion for statistical significance was an alpha level of 0.05.

3.9. Summary

This chapter has presented the theoretical framework underpinning this doctoral research. Study 1 and Study 2 are explained separately (and in detail) in Chapter 4 and 6, respectively. The discussion

of these two studies' results is presented in Chapter 5 and 7, respectively. The findings from the two studies are triangulated before conclusions are drawn in Chapter 8.

4. Chapter 4 Study 1. Pain in childhood leukaemia: experiences of parents and clinicians

4.1. Overview of Chapter 4

This chapter provides a review of Study 1. The first section outlines the methods of the first study. The following section addresses research quality and ethical considerations. Finally, interview findings are reviewed.

4.2. Methods

In this study, a qualitative approach was used to explore how parents and HCPs experience and manage pain in children with ALL.

4.2.1. Participants

Mothers and fathers of children with ALL and nurses and doctors involved in the treatment of those children at paediatric oncology department and PICU were purposively sampled (section 3.6). This sampling strategy was chosen to ensure diversity in the characteristics and perspectives of the participants: different parental roles (mothers and fathers), professions (nurses and doctors) and medical specialties (paediatric oncology and PICU).

Children with ALL are treated by a number of HCPs from multiple disciplines. Among these, the doctors and nurses at the paediatric oncology departments are responsible for most diagnostic and therapeutic procedures. Furthermore, some children with ALL may experience severe complications that require admission to an intensive care unit, where dedicated doctors and nurses provide specialised care in collaboration with paediatric oncologists. Doctors working at Danish intensive care units are anaesthetists with a special interest and training in intensive care medicine. Also, nurses working at intensive care units have skills to manage both acute critical illness and palliative care at the end of life (Jones et al., 2020). Nurses and doctors at the paediatric oncology department and PICU were sampled because they are responsible for a child's treatment during longer periods of time: the treatment of ALL takes 2-3 years while an admission to PICU lasts a few days up to several weeks. Other medical specialties (e.g., surgery, radiology) may provide important diagnostic and therapeutic support but have typically a shorter contact to children and families and were therefore not included in this study. Nurses and doctors taking care of children with ALL at paediatric oncology department and PICU play a key role in identifying and responding to children's symptoms that include medical, emotional and social support (Colville, 2012; Zhukovsky

et al., 2015) (section 3.4.1). Several studies have focused on nurses' challenges (Linder & Wawrzynski, 2018) but only a few studies have examined nurses' and doctors' perspectives (Forsey et al., 2013). Moreover, research frequently addresses only one medical specialty (e.g., oncologists) (Levine et al., 2019). However, HCPs at PICU treat the child and family in an acute situation when the child is critically ill and may have different perspectives on a child's pain experience.

During the course of ALL, parents play an important role in influencing child and family adjustment to childhood severe illness (Kazak & Barakat, 1997). While most of the research looking at the impact of illness on the child and family has focused on maternal experiences (Earle et al., 2007), there is only a small body of work that has emphasised the role of fathers in family adjustment to a child's severe illness (Hill et al., 2009; McGrath & Chesler, 2004b) (section 2.6). In this study, the perspectives of mothers of fathers were equally included, aiming to provide a balanced parental perspective (inclusion criteria are presented later in this section). Based on a biopsychosocial framework for care, this study sought to explore the perspectives of mothers and fathers as well as nurses and doctors that were involved in a child's care during ALL treatment at the paediatric oncology department and PICU.

Study 1 was conducted at the paediatric oncology department and PICU at Aarhus University Hospital, Denmark, between June 2017 and November 2019.

Inclusion criteria for parents

A trend towards treatment being the primary cause of pain for children with cancer has been found in background literature (Twycross, Parker, et al., 2015), so the decision was made to include parents whose children with ALL were on treatment with a curative intent, as pain manifestation and management differ in advanced cancer (Van Cleve et al., 2011). Furthermore, the children had to be boys and girls aged 1-18 years old as this age group was treated according to the same treatment protocol presented in section 2.2.2. and had to include children three to five years old as ALL most often occurs in this age group (demographic data are presented in section 4.6.1).

An equal number of mothers and fathers were interviewed to reflect possible differences in female versus male parental perceptions (one parent/child)

Exclusion criteria for parents

Parents were excluded if they had insufficient language capacity to complete an interview.

Inclusion criteria for clinicians

The inclusion criteria were working as a registered nurse or a consultant at the paediatric oncology department or paediatric intensive care unit, with an equal distribution of nurses and doctors from the two departments.

Exclusion criteria for clinicians

Nurses and doctors, who did not treat children with ALL were excluded from this study.

Recruitment strategy

In general, participants were chosen on the basis of their close involvement with the child`s care and therefore relevance to the understanding of the child´s pain. Thus the recruitment strategy was closely related to the sampling approach.

Parents, nurses and doctors were recruited using various methods that included an introductory letter, recruitment posters on the ward, e-mails sent to clinicians and an introduction to the study during staff meetings.

4.2.2. Data collection tool

Data was obtained through semi-structured interviews conducted one-to-one and face-to-face, which enabled the interviewer to confirm that participants understood the questions and allowed them to express their experience in a flexible and informal manner (Braun & Clarke, 2013b). Face-to-face contact between researcher and participant has typically been viewed as the “gold standard” to collect interview data. Nonverbal data such as facial expressions and body language as well as contextual information about the environment and the physical features of the respondent can contain cognitive or emotional content, which are thought to contribute to the richness of data and the interpretation of participants’ verbal responses (Fitzpatrick & Boulton, 1994).

4.2.3. Procedure

The interview-guide

Conducting a qualitative study required the development of a data collection instrument, in this case an interview guide, which related to the research question. The questions in the interview guide focused on giving a voice to parents' and HCPs' experiences with child's pain during ALL. These experiences are multifaceted and involve the entire family throughout the diagnosis and treatment process (Molinaro & Fletcher, 2018). A child's pain is related to both the disease and treatment and insufficient pain relief impacts on the quality of life of the child and parents (Woodgate & Degner, 2003). The undertreatment of pain may be related to the concerns, beliefs and sometimes misunderstandings of parents and medical staff. Beliefs about health and medicine emerge primarily from an individual's education and knowledge, together with the influence health care providers exert on their patients (Sitaresmi et al., 2010). Understanding parents' and clinicians' perspectives regarding pain assessment and management in childhood ALL may identify issues important for pain alleviation that are not yet addressed by current research.

The questions in the interview guide were developed from studies that investigated similar issues (Enskär, Carlsson, Von Essen, et al., 1997; Hedén et al., 2013). Questions were defined by the researcher and verified with the supervisory team. The questions in the interview guide were considered from both parents' and clinicians' perspectives. Interview topic guides for parents and HCPs are presented in Appendix 3 and 4, respectively.

Conducting the interviews

The location of interviews is important to make the participants feel comfortable and the researcher feel safe (Braun & Clarke, 2013b). Moreover, the choice of location supports the maintaining confidentiality. Therefore, in this study, the interviews took place in a quiet office in the hospital and lasted on average 30 minutes (SD= 5.12, range 25-40).

Interviews commenced with the researcher explaining the interview contents and reminding participants that there were no right or wrong answers, ensuring again that they understood their right to withdraw (Braun & Clarke, 2013b). In a short introductory section, the interviewee was asked to state their role and explain in brief their experience with children's pain. This was undertaken to create a comfortable atmosphere. Next, questions addressed issues relating to

experience and knowledge, allowed the participant and researcher to build rapport, gave participants freedom to tell their story, and provided the researcher with context for the remainder of the interview (Green & Thorogood, 2014b). Parents were encouraged to discuss their child's disease, therefore generating a natural platform for further questions. The first topic was regarding pain assessment, severity and characteristics of pain. This part also included a question asking participants to describe when they thought a child/their child was in pain. This question sought to understand what signs of pain they looked for in a child/their child (e. g., different behaviours). The following topic was related to decisions to relieve this pain and how they were made. This was followed by questions regarding special challenges the participants experienced with a child/their child's pain. In addition, the interview-guide for clinicians included questions about the documentation of pain and the use of pain guidelines. Towards the end of the interview, questions were asked addressing more sensitive topics such as opinions, relationships and feelings. Prompts were used to clarify and test assumptions and keep discussions on track (Green & Thorogood, 2014b). Finally, all participants were encouraged to ask questions and discuss relevant issues that had not been covered by the interview -guide.

A researcher follows an interview guide to stay on topic, while also leaving room for exploring certain paths when the interviewee directs the conversation (Braun & Clarke, 2013b). This is an important aspect of the semi-structured interview guide as it facilitates the understanding of the phenomenon and for this to happen, participants should be allowed to explain their complete perspective openly. In other words, this means the researcher further explores areas that are worth exploring (Fitzpatrick & Boulton, 1994).

4.3. Quality in qualitative research

Various criteria have been developed to both ensure and judge the quality of qualitative research (Braun & Clarke, 2013c). Yardley suggested some open-ended, flexible principles as a guide to ensure the quality: sensitivity to context; commitment and rigour; transparency and coherence; impact and importance (Yardley, 2000). Furthermore, to emphasise quality in qualitative research, Elliott suggested guidelines for publishing: 1) Owning one's perspective 2) Situating the sample 3) Grounding in examples 4) Providing credibility checks 5) Coherence 6) Accomplishing general versus specifically research tasks and 7) Resonating with readers (Elliott et al., 1999).

To ensure quality, this study has focused on multiple sources of evidence from multiple interviews. Moreover, a supervisory team reviewed the interview guide and the quality of findings. Cross coding a part of the interviews enabled a discussion between the researcher and supervisors (Green & Thorogood, 2014a). In addition, the researcher chose to implement a process of double coding, where a set of data was coded, and then after a period of time the researcher returned and coded the same data set and compared the results (Baxter & Jack, 2008). Finally, the approach used to increase faith in credibility was to provide enough context for the reader to judge interpretations- such as details of the project and inclusion of raw data (Green & Thorogood, 2014a).

4.3.1. Reflexivity

To increase rigour, reflexivity was implemented throughout the study. This is a major strategy for quality control in qualitative research, as qualitative data result from interactions between participants and researcher (Berger, 2015). Researchers alter data collection in relation to their input to interactions. Reflexivity is the practice of identifying how a researchers' presence, actions and beliefs impacts on data. Reflexivity accounts for researcher bias and transforms subjectivity into a positive tool (Berger, 2015). In this research, reflexivity was exercised through frequent discussions with the supervisory team, reflecting on actions and considering personal prejudices and assumptions throughout data collection.

4.4. Ethical considerations

4.4.1. Ethical approval

University Ethics Approval for the PD study was gained from the Research Ethics Committee for Health at the University of Bath (REACH) on the 13.10.2016 with reference EP 16/17 035.

For the current qualitative study, the researcher also submitted the study protocol, materials and participants' documents to the Central Denmark Region Committee in Biomedical and Research Ethics and they deemed ethical review was not necessary for a qualitative study (Appendix 1). The study respects the Privacy Act and has received approval from Data Protection Agency in Central Region Denmark on the 26.10.2016 with reference 1-16-02-579-16 (Appendix 2).

4.4.2. Informed consent

Written informed consent was obtained from interview participants (Health Research Authority, 2019). A combination of written and verbal information (e.g. information sheets and the chance to ask the researcher questions in person) was provided to enable participants to make a truly informed decision (Green & Thorogood, 2014b). Written information was clear and concise with a level of detail which provided important information but was not overwhelming. Verbal information was open and honest and followed similar principles without the researcher coercing or applying pressure on participants (Braun & Clarke, 2013b). Effort was made to ensure that participants fully understood their right to withdraw (Green & Thorogood, 2014b). Participants were given adequate time between receiving information and commencing participation to allow them to consider their involvement and identify areas which may require clarification (Green & Thorogood, 2014b).

4.4.3. Anonymity and Confidentiality

Procedures were designed to promote participant anonymity and confidentiality. Identifiable information was not collected during the interviews. Confidentiality was ensured by storing information securely in a locked cabinet. Only the researcher had access to any potentially identifiable data. Participants were assigned a unique ID to aid analysis whilst maintaining confidentiality (Green & Thorogood, 2014b). Identifiable information was removed from transcripts. Participants could conceivably be able to identify themselves in quotes used in publications but identifiable information was removed, so readers from the general public would not be able to identify participants. Secure destruction of research data will be performed after publication according to the rules of Data Protection Agency in Central Region Denmark.

4.4.4. Ethical conduct in qualitative research interviews

Involvement in research can have emotional consequences, especially when research concerns experiences involving a sensitive topic such as pain in children with ALL. Being cognisant of the emotional consequences of being involved in research, the researcher used strategies to minimise harm (Green & Thorogood, 2014b). Attention was given to building rapport through attention, interest and humour and being responsive to mood and mindful of posture. A flexible approach was taken to personal sharing or disclosures and attention was given to the language used (Green &

Thorogood, 2014b). Interviews were conducted with awareness that the researcher was not part of the study population (Berger, 2015).

During interviews, parents were vulnerable, due to the burden of having a child with leukaemia and potentially distressed when thinking about their child's pain (Molinaro & Fletcher, 2018). Clinicians could also be vulnerable due to moral distress (Burston & Tuckett, 2013). Listening to untold stories and feelings of vulnerability may be exhausting for the researcher and the interviewees. Techniques to reduce emotional distress included showing empathy, allowing silence, moving on from distressing subjects, and creating breaks (Dickson-Swift et al., 2007). The researcher was aware of local procedures to access support for participants, including psychologists and experienced staff on the ward. Participants were made aware of this prior to commencing interviews.

The relationship between researcher and participant is typically conceived as a hierarchical one, with the researcher in control of the interview (Braun & Clarke, 2013b). This interviewer - participant hierarchy was challenged through a process of empathic interviewing. In addition, the dual role of the interviewer as a doctor and researcher may have caused problems for participants (Berger, 2015). Participants may have known the researcher and consequently felt obliged to participate. The strategy implemented to minimise this possibility was to provide information, emphasising the voluntary nature of participation. For parents, the distributed information highlighted that participation or lack thereof would not affect their child's care. Knowledge that the researcher was a doctor may have meant participants asked questions outside the scope of the study (Braun & Clarke, 2013b). Participants were treated with respect and questions outside the scope of the study were answered but not included in the transcripts.

4.5. Data management and analysis

Braun and Clarke's inductive reflexive thematic analysis was used to analyse the qualitative interview data (Braun & Clarke, 2019). Reflexive thematic analysis is a systematic, rigorous and theoretically flexible method that has been used for organising, describing and interpreting data in health research (Williams et al., 2020). For example, in paediatric research, this method was used to analyse interviews with children and their parents regarding quality of life in palliative care (Gaab, 2015) and juvenile arthritis (Sen et al., 2017).

The technique was developed in the 1970s but has only recently been recognised as a distinctive method with a clearly outlined set of procedures (Braun & Clarke, 2006, 2013a). Braun and Clarke's reflexive version of thematic analysis was chosen since it provided a straight-forward step-by-step process for conducting a transparent and thorough analysis. Moreover, this method offered a robust framework for coding interview data and for using that coding to identify patterns across the data set in relation to the research question (Braun & Clarke, 2019). The focus on patterning of meanings across participants was essential in this mixed-methods research study which focused on investigating the experiences of different informants with a broad diversity of perspectives and views on a child's pain.

Furthermore, Braun & Clarke's (2019) reflexive thematic analysis approach emphasises the interactive process between data, the researcher and the context of the research itself. The reflexive thematic analysis themes are conceptualised as analytical outputs created from codes through the researcher's active engagement with their data. Using this technique, the researcher sought to create the findings from the interview data through the process of analysis. This process required a reflexive researcher (section 8.7.), who strived to reflect on the assumptions made throughout this analytic work that was shaped by the researcher's subjectivity based on her views, skills and experience as a paediatric anaesthetist.

As outlined by Braun and Clarke (2013a), after the transcribing process the analysis was conducted in six stages: reading and familiarisation, coding, searching for themes, reviewing the themes, defining and naming themes and writing final analysis.

4.5.1. Transcribing process

Interviews were recorded in the spoken language, which was Danish. The recordings were transcribed verbatim soon after the interview was completed so that the experience was still recent and details were easier to capture. Hesitations and other irrelevant wording, such as the interviewer's listening responses and affirmations were removed from the transcribing process.

The transcripts were translated from Danish to English by the researcher. A Danish research assistant with good English language skills was consulted to check the translated transcripts. The supervisory team checked language nuances for different terms.

4.5.2. Familiarisation with data

The analysis of data began with a process of "immersion" into the data to help the researcher become familiar with the content (Braun & Clarke, 2013a). Familiarisation with data was not just a passive understanding of the words in the interviews but an active process that involved reading the data attentively, analytically and critically. This stage made the researcher reflect about what the data meant and what feelings the participants might experience in relation to a child's pain in the context of living with ALL. Moreover, the researcher started the work of developing an analytic sensibility, which refers to the skill of reading and interpreting data through the particular lens of the chosen method, in this case thematic analysis. Braun &Clarke (2019) specified that because thematic analysis is just a method and its hallmark is flexibility, it can be used widely across the epistemological and ontological spectrum.

4.5.3. Coding

The computer assisted qualitative data analysis tool NVivo 11 (Bazeley & Jackson, 2013) was utilized to index and sort the data by applying nodes (codes) and organise the codes into themes (Green & Thorogood, 2014a).

Coding is the process by which raw data is converted into concepts that have a connection to the study aim (Braun & Clarke, 2013a). There are two main types of coding, selective and complete. Selective coding is where only certain parts of the data are coded in relation to a particular phenomenon of interest to the researcher. Complete coding aims to capture anything that is relevant to the study topic within the entire data (Braun & Clarke, 2013a). In the first phase, complete coding was adopted, followed later by a more selective approach as coding is an organic and evolving process (e.g., conversations around participants' background have not been coded).

4.5.4. Searching for themes

In this research study, the use of a thematic analytical approach involved searching the data for repeated patterns and understanding how they fit within the dataset to tell a story (Braun & Clarke, 2013a). The reflexive version of thematic analysis, which was used in this study, contrasts with other analytic approaches, such as codebook or coding reliability approaches. Codebook approaches can use a codebook to chart or map the developing analysis (Ritchie & Spencer, 2010). Coding reliability approaches are based on a structured coding frame, multiple independent coders

and the measurement of coding reliability (Boyatzis, 1998). Braun & Clarke (2019) do not advocate this approach because they feel coding reliability measures are in fact imposing a positivist framework onto qualitative research methods.

The technique used in this research was flexible and coding was an active and reflexive process (Braun & Clarke, 2019). The researcher started the analysis by utilising deductive coding in which categories from previous literature shaped the interview guide and initiated the categories in which data was placed. During the coding process, patterns were identified across all the data items and over time, inductive coding led to the generation of different themes. For example, codes like "pain as a sign for different conditions", "fear of death" and "dealing with parental anxiety" generated the theme "anxiety and fear for the unknown". The development of themes required considerable analytical work on the part of the researcher, including the construction of mind-maps which aided in the visualisation, organisation and interpretation of the codes into themes. Interpretation of data was facilitated by identifying further patterns, links, similarities and differences in the participants' perspectives.

4.5.5. Reviewing the themes

This phase included revision of all the coded and collated data to ascertain that each theme was captured. The themes were reorganised and reoriented to create a better data-fit as the themes needed to both be distinctive in their own right yet also work together (Braun & Clarke, 2013a). Moreover, the process of reviewing the themes included a final re-read of all items. This procedure ensured that the individual themes captured the meaning of the data set in relation to the research question of this doctoral programme.

4.5.6. Defining and naming the themes

Discussing the data with the supervisory team supported the identification and organisation of themes. Defining themes was an interactive process that involved working out the scope and the "story" of each theme. Names for the themes were chosen to be easily understandable and to capture the essence of the theme's focus.

4.5.7. Analysis report

A report of the analysis is written as a story of the data related to the study topic, including the researcher's interpretations and illustrative extracts. Extracts from interviews are used to describe

each theme more accurately. All extracts are presented in italics and any comments by the researcher are presented in bold. Parts of the sentence which have been removed to reduce length are presented with ellipses. Research participants were provided with an ID: a letter (P for parent, N for nurse and D for doctor) and a number, whereas participants' children were given a pseudonym in the transcripts.

4.6. Results

4.6.1. Participants

Sixteen participants agreed to be interviewed regarding their experiences with a child/their child's pain and gave their written consent. The parents were three mothers and three fathers of six children with ALL (one parent/child). These children were two boys and four girls on average 10 years old (SD=4.8, range 4-17 years) and 1.1 year (SD=0.5, range 0.9-1.5 years) after the diagnosis and with expected curability of disease. Clinicians who participated in this study were all females and had been working in a clinical setting for 21 years (SD=3, range 17-25). Of these years, at least five involved working with paediatric oncology patients. Six nurses and four doctors from the paediatric oncology department and PICU participated in this study, as illustrated in Table 4.1.

Table 4.1.

Participants overview

Participants			**Number**
Parents	Mothers		3
	Fathers		3
HCP	Nurses	Paediatric oncology	3
		PICU	3
	Doctors	Paediatric oncology	2
		PICU	2
			16

Note: HCPs=health care professionals; PICU= paediatric intensive care unit

4.6.2. Thematic analysis findings

Three main themes each with 2-3 subthemes were created from the codes generated from the transcripts of the interviews and are illustrated in Table 4.2.

Table 4.2

Themes and sub-themes

Themes	Subthemes
Complexity of pain assessment	Signs of pain
	Getting pain assessment "right"
Anxiety and fear for the unknown	Pain as a mask for psychological distress
	Clinicians' concerns and uncertainty
	Parental concerns for strong medication
Empowering families	Relationship with families
	Decision making
	Child-parent coping

Themes and subthemes are linked with each other, illustrating the large variability of factors that influence a child's experience of pain and how this is experienced, understood and managed by parents and HCPs. The themes are presented individually and the linkages between themes/subthemes are mentioned, when relevant, along with interview findings.

4.6.2.1. Complexity of pain assessment

This theme outlines the manifestation of a child's pain and experience of symptoms during ALL. This topic also highlights how parents, nurses and doctors understand a child's expression of pain and how this influences their assessment.

Signs of pain

This subtheme is about manifestation and recognition of pain. Participants described the multifactorial nature of pain, noting that this is caused by multiple physical factors including disease, adverse reactions to treatment and painful procedures. Pain had a strong impact on a child's behaviour:

> *"Small children cry, or they don't want to eat. Some of them are restless and some of them lay down and do not move. "D3*

Awareness that the child underwent a treatment known to be painful made HCPs look for signs of pain. HCPs described how pain assessment was influenced by their knowledge of pain and the disease process and included observations of the children's reactions as well as parental responses:

> "*I think a child is in pain when he or she changes behaviour but also when I know that the child undergoes a treatment which causes pain. I think of pain when I give chemotherapy because I know there are some adverse reactions such as mucositis." N1*

Parents developed alternative ways of understanding their child during ALL. Thus, they reported various ways of knowing when their child was in pain including attending to their child's behavioural and verbal cues, mood, body language and circumstances. Parents felt they knew their child so well that they could recognise when the child was in pain. Several parents reported that their child became quiet and did not talk or play, often withdrawing physically and trying to be alone:

> *"I know precisely when she is in pain. She is still, she does not want to do anything or communicate. "P5*

Parents reported that their children experienced severe pain and other distressing symptoms related to treatment. Children felt pain in many parts of their body including the jaw, head, legs, back and stomach. Frequently, children experienced mouth and throat pain due to mucositis. Parents also described that their children had thin and sensitive skin and could barely be touched. Sometimes complications occurred, and the children were admitted to PICU:

> "*She suffered from several infections and severe inflammation of the intestines. She was very constipated. She needed surgery in the middle of the night because the anal wound was bleeding. After surgery she stayed at PICU for one week. She was very much in pain. She received iv medicine… was very tired, slept most of the time…she had delirium while she was in the PICU. She saw crabs all over. P4*

During their stay at PICU, pain and other symptoms were aggravated due to intensive treatment and

multiple procedures. Having a child in pain and with delirium was very distressful for parents:

> *"The adverse reactions to the treatments were the most distressing: intensive delirium, convulsions, allergy, infections, you name it… He had pain in the bones and joints and muscles, everywhere. The whole body ached." P2*

HCPs emphasised that pain assessment was particularly important as this had implications for both diagnosis and pain management decisions. Therefore, pain may suggest different serious conditions that need different treatments:

> *"Abdominal pain can be just pain or constipation, nausea or too much acid in the stomach. Their symptoms may require different medication." D1*

In addition, the management of chemotherapy side effects needed great attention as these could be extremely serious, even life-threatening. Some cases needed deep sedation while waiting for recovery:

> *"complex children with cancer may be in very severe pain… the bowel is doubled in size, and they have severe cramps… We have to give them so much pain medication; if you and I got so much we couldn't breathe anymore." D4*

Unprompted by the interview questions, parents described several other distressing symptoms experienced by their children, which inter-related with pain. Muscle weakness was common, because of the underlying illness or as a side-effect to strong analgesics. Parents reported that children lacked energy and spent lots of time sleeping and resting:

> *"He was so weak that he couldn't turn in bed…we had to help him to turn him from one side to another. He could not even move under the blanket." P2*

Nausea was another frequent symptom and was often accompanied by pain. Parents described that long-lasting nausea affected their child's condition and was sometimes a major concern:

> *"He had pain in his bones and muscles, nausea and vomiting…it was terrible." P3*

HCPs often commented regarding a child's age as both a positive and negative contextual factor. They described an older age as advantageous since it provided the child with the ability to reason

and communicate regarding their pain. Good dialogue with the children about their pain and other issues made the process of pain assessment easier for clinicians. HCPs commented that when the child understood the pain scoring then they could be more readily involved in pain management decisions. A constructive dialogue with children was central for HCPs:

> *"It is easier with the older children since they can localise and describe the pain. It is easier for the staff to use these comments and the pain scorings to decide how to go on with the pain management." D4*

In contrast, HCPs described the challenges they encountered when small children could not describe the symptoms and parental interpretation was the main source of information:

> *"It is so difficult to understand pain, that is why we involve the parents especially for small children. "D1*

However, HCPs reported that very young children, 2-3 years old, could say they were in pain or just point at the painful part of their body. Children have their own views and perspectives and could speak for themselves if the appropriate methods were used:

> *"Very early, normally when they are three years old but also two years. They can say that they have pain in their belly. Or just point at the belly. They can have their own meaning about things. Sometimes difficult to interpret but still they have their own meaning." D1*

Small children had sometimes their own "language" to describe pain and distress: when asked about pain they could talk about something totally different:

> "*They may say "I am in pain" because this is easier to describe. They call for help and then they talk about something totally different like a horse or a game. "D1*

HCPs explained that psychosocial factors could additionally influence their assessment in a major way and make them uncertain as to what was perhaps normal behaviour and what was due to disease or medication. It required time and a good knowledge of the family to correctly assess symptoms:

> "*What is their normal behaviour and when do they behave as they do because of their disease or their medicine? Or is it because they cannot cope with the situation? So, it is important for me as a nurse to have the time to be with the child and family and assess their behaviour. To have the time to listen and understand how they cope with the condition." N1*

HCPs addressed the fact that a child´s pain expression is multifaceted and depends on a child´s bio-psycho-social background as well as how the people around the child (parents, peers, HCPs) interprets this pain. These factors contribute to the complexity of getting pain assessment "right" as further discussed in the next subtheme.

Getting pain assessment right

This subtheme highlights HCPs' focus on getting a "correct" pain assessment. This is linked to the subtheme "signs of pain", where the importance of pain assessment for diagnosis and treatment decisions has been outlined. HCPs emphasised that education, pain guidelines, relevant documentation, teamwork and time to listen to the families were key factors for better knowledge regarding pain and to enable appropriate pain assessment and management. HCPs reported that there were various age appropriate pain scales available on the ward, and some of the participants were supervisors for other less experienced clinicians. HCPs explained how they performed a correct pain assessment according to local guidelines; how they wanted to get an insight into a child´s history and pain issues and start a dialogue regarding pain relief strategies:

> *"I ask the child about the history: Where is the pain? How intense is it? And ask the child to score the pain according to our scoring systems. We have both the FLACC score and VAS score. I also ask them to tell me what relieves the pain. I mean other things than medicine, what they usually do." N5*

When HCPs described the use and usefulness of pain guidelines, they also mentioned that there were differences in the way these guidelines were followed. Nurses routinely assessed pain but not always documented it according to validated tools, they would describe it in their own words. Moreover, doctors reported that they assessed pain but rarely documented pain scores:

> *"We can use pain scales but generally doctors are not so good at using them. I try to describe it if it is a long-lasting pain or breakthrough pain or snoring pain or*

cramps… No, I'm not so good at it; I have used it once during a project, but I do not use it daily." D3

An important issue highlighted by the HCPs was that they seldom documented the effect of pain management. They argued that a busy work programme led to different priorities:

"I think we are good enough at asking about pain and maybe start pain treatment, but I do not think we are good enough at documenting and evaluating the effect of pain management. Although pain scores are easy tools they are not used sufficiently. Sometimes it is just the nurses' evaluation. If it is difficult to make the child score on a pain score, then the nurses do not do it. I think the nurses are in a hurry and do not see the evaluation of pain and pain management as a priority." N5

Nurses routinely educated children and parents in the use of an appropriate pain scale for the child´s age. However, parents seldom used the pain scales and expressed a range of reasons why they did not: they believed children were too young or too tired or that they did not need pain scales to recognise pain. HCP explained that the consequence of inadequate pain assessment was undertreatment of pain and a high score would suggest that pain relief was needed.

"*When you see a child with a high pain score let's say 7 or higher on a pain scale 0-10 then you must act and give some painkillers." N2*

HCPs generally understood the responsibility for optimising pain management and appreciating the specific nature and characteristics of each situation and that all children are different. The uniqueness of each child with leukaemia was a key concept for HCPs. Each child has different pain manifestations, feelings and emotions when being exposed to hospitalisation and treatment; they acquired their own experience with pain and other symptoms. The idea that pain experience was unique for each child was highlighted by HCPs as a permanent challenge:

"It is difficult every time. Every single time. Each story is different." N3

This led to a greater awareness for the need to perform correct individual pain assessment and management but was also a source of doubt and uncertainty for HCPs, since guidelines did not address it:

> "*Sometimes I underestimate… I am a little restrictive not because I don't want to relieve pain, but I want that the assessment of pain to be as correct as possible". D1*

Clinicians' concerns about correct assessment and management of pain was a common issue, which linked together this subtheme with the next theme: anxiety and fear for the unknown. Thus, HCPs supporting each other as a team might help to alleviate some of the uncertainty and anxiety that HCPs reported about pain management.

> *"I think it is about not feeling alone, you need to feel someone supports you, there is collaboration regarding how much medicine I can give. And that the plan is made by experienced doctors, a plan that you can rely on and it will not be changed when someone else comes." N4*

4.6.2.2. Anxiety and fear for the unknown

This theme is about children's and parents' anxiety and the influence of previous pain experiences on present and future pain experience. Complex past pain experiences may require a good knowledge of children and families. This knowledge is essential for creating individually tailored pain relief strategies as well as for understanding parents' and clinicians' worries regarding pain management.

Pain as a mask for psychological distress

This subtheme focusses on psychological distress and pain.

Parents and HCPs agreed on pain caused by physical factors associated with the experience of ALL. However, interestingly, HCPs and parents perceived emotional distress associated with ALL related pain differently, with HCPs referring to such pain as "pain due to psychological distress". This type of pain appeared to be more important for nurses and doctors than for parents. HCPs perceived "pain due to psychological distress", as a result from the complex interaction of psychosocial factors, such as a child´s developmental status, past pain and anxiety experiences and the complex role of parental understanding and coping with a given child's disease circumstances.

HCPs described that generally, older children expressed more pain than younger children. They attributed this to various developmental and psychosocial factors. However, when older children expressed higher than anticipated levels of pain, HCPs perceived this as a considerable challenge.

Was the issue about physical pain or was pain a mask for other things such as distress, anxiety and fear of the unknown?

> *"Sometimes they lie in bed with their head under the pillow and they don't want to talk. They are sad and depressed. It is easier to say "I am in pain" than express feelings. We have had some unpleasant cases where we treated pain due to psychological distress with painkillers. Difficult to interpret." D1*

Children's levels of distress were a source of concern for HCPs, as pain could be either related to psychological issues or complications of treatment. There were substantial differences across HCPs in management strategies regarding these issues and understanding the cause of pain was sometimes difficult; family conflicts were especially difficult to talk about with the child:

> *"Children with pain due to psychological distress are often children exposed to conflicts. Either due to problems or complications during the treatment or conflicts in the family. It feels like all conflicts move into the child's belly." D1*

HCPs commented that pain, anxiety and fear of the unknown played a role in each child´s disease experience. However, differentiating between fear and pain was a key challenge in making a pain assessment as children with ALL experience many fear-provoking circumstances during their treatment. Generally, the recognition and treatment of anxiety was expressed by HCPs as a major component in the treatment of a child´s pain experience. In this context, HCPs stressed the importance of minimising a child´s anxiety, both before and during procedures and generally throughout the treatment. HCPs reflected on ways they could focus more on a child's anxiety and advocated for the broader use of strategies to potentially prevent it:

> *"I think it will influence the children's experience of pain if we get better at treating their anxiety before and during procedures… You know, if they get more relaxed before procedures and not so nervous. I think the pain experience will be diminished if they experience less anxiety. "N5*

HCPs described that children who experienced a high level of pain and anxiety during an initial procedure were at risk of experiencing higher pain during subsequent procedures. This could have a long-term effect on a child´s pain experiences:

> *"When I look at the history in the medical record, I can see that children with very intense pain complaints have previously experienced many painful procedures with insufficient pain relief. They are afraid of everything; they suffer from anxiety and cannot sleep. I am talking about the memory of pain and how pain experiences influence the child later also even as a grown-up." N2*

Complex pain experiences and the subjective nature of every child´s pain might therefore require HCPs to individually tailor pain relief strategies. This requires comprehensive documentation of past experiences and pain treatment. HCPs stressed that providing relevant and complete information in the medical record needs to be a priority for children with leukaemia:

> *"I know perfectly well that there is a time factor, but when we talk about leukaemia children, who undergo a two-year long treatment, I think it is essential, that you have a good description in the medical record regarding ongoing pain management, anaesthesia requirements for procedures. That would be great." N3*

Both children and parents experienced anxiety and fear during ALL treatment. Sometimes, parental anxiety could be so high and overwhelming that it influenced the parent´s ability to support their child during treatment. HCPs perceived high parental anxiety as a source of distress requiring greater attention and resources to manage. Providing parents with adequate information regarding the treatment plan and methods that involved them distracting the child (e.g. playing with them or singing a song) empowered parents to be more supportive. Therefore, the subtheme regarding fear and anxiety was linked to other key topics such as the HCPs' relationship with families and their ability to help the families cope with their child's illness.

When ALL children were admitted to the PICU, clinicians working there experienced that children with leukaemia had a longer illness history and were more distressed and sensitive to pain compared to children with other chronic illnesses. They attributed the higher level of distress in children with ALL to multiple previous experiences of painful procedures, which were especially traumatic due to the perceived inadequate management of pain and anxiety:

> *"I clearly feel that they have a history … with different anxiety provoking experiences for them and the parents. There have been procedures where the children for example, have*

> *said no, and it still had to be done, so for both parents and children there have been, what you could call extremely traumatic experiences." N3*

Furthermore, the children admitted to the PICU experienced more pain from the side-effects and complications of treatment as well as the multiplicity of procedures. Facing a life-threatening condition daily increased the child's and parents' levels of anxiety overall as well as the fear of further suffering and ultimate death. HCPs explained that there were differences between their understanding and the families' understanding of the child´s illness and its severity. Some families had a low acceptance of illness; others constantly feared that their child would die and believed everything should be done to avoid suffering. These feelings challenged HCPs and their collaboration with families:

> *"Children with leukaemia admitted to the PICU often have a severe physical pain problem, but sometimes other factors have made the pain worse… they have a severe disorder associated with a major fear of death… We have children who are very anxious and children who have difficulties in understanding they are very ill. We have some parents and relatives who are generally very tense, they are under the intense ongoing pressure of having a child who is so ill." N3*

A factor that was common for all parents in this study was that they believed their child would be cured. However, when prompted by an interview question regarding the greatest challenges in a child's treatment, parents described that they often felt anxious and feared that their child's condition would be aggravated. Parents also reported being quite afraid that their child might die from leukaemia. For some parents, the fear of losing the child was often related to the possibility of acute complications, such as from surgery, severe infections, convulsions or bleeding:

> *"When she needed surgery in the middle of the night. I thought I would lose my daughter. Because it was very acute. I feared she would die." P4*

For other parents, fearing a child's death was constant because they experienced a problematic disease trajectory:

> *"The greatest challenge was that we were constantly afraid of losing him. For the first 7-8 months everything was challenging." P3*

One parent expressed fear of their own death and therefore not being there anymore to take care of the child:

> *"I felt a deep anxiety: what would happen to my daughter if I died and could not take care of her anymore? Maybe a combination, I was afraid of losing her, or that she would lose me." P6*

Clinicians' concerns and uncertainty

This subtheme addresses HCPs concerns about best practice for managing pain in children with ALL.

Pain was a symptom that had psychological implications for parents. Many children experienced pain as a symptom associated with complications, such that when the child was in pain, parents feared their child's condition might further deteriorate, or the child could even die. The reaction of some families to anxiety was sometimes an intense focus on their child's pain and request for stronger pain medication. Such requests were sometimes perceived cautiously by HCPs when children requested higher doses of opioids than HCPs considered that the children needed:

> *"Usually, I try to find out from the child's past history. But it is sometimes difficult to find out. Do I need to give more morphine, or do I need to say: no, you do not get more because you do not use it for pain but because you are distressed? Then you can do something else to feel better. "N1*

Nevertheless, in most cases, children's and parents' descriptions of pain and requests for pain relief corresponded to clinicians' assessments and were perceived by HCPs as beneficial for the child. Generally, HCPs attempted as best as possible to follow parental needs and wishes during a child´s treatment. However, high parental anxiety could sometimes lead to a difference in pain estimation and expectations compared to HCPs and consequently generated a conflict of opinions.

> *"Sometimes, we need to explain to the parents that we might need to change the direction and plan of treatment. We cannot always follow their wishes … One of the cases was quite demanding due to maternal lack of understanding that the nurses could not be by her child all the time and she asked constantly for stronger pain medication and benzodiazepines. It was very difficult." D3*

The interactions between parents and HCPs need to be about optimising the child's treatment and alleviating distressing symptoms but it might sometimes also feel difficult.

> *"Collaboration with parents … is challenging and exciting, too, when it works. Sometimes however it's stressful… we cannot say, "I do not want to take care of this very ill child" or "I cannot talk to these frustrated parents". N4*

The HCP/parent relationship might consequently feel very precarious and fragile at times. A good interaction could deteriorate quickly due to the specific situation at the time, especially when parents were frustrated because their child was distressed. HCPs highlighted the role that parents played in their ability to offer clear communication and how the parents could alter the mood and make it more challenging for HCPs to communicate. Furthermore, HCPs explained the difference between child and parental distress and the distress experienced by HCPs: parents and children were both consumed by their distress. It was distressing for HCPs too, however this was their job, so they were not quite as consumed. Poor communication with parents created uncertainty and distress:

> *"I think the most challenging thing is to be credible, convincing, saying that we have it under control and this will be good for your child. These families have been through so much. We meet some parents who do not feel they have been listened to. And we have parents who say we are not doing enough; they want us to give more pain medication, and that we, somehow, must figure out how to find something that will make their child feel better. It feels like an enormous pressure." N3*

HCPs described the fear of "not doing enough" when they had a difficult patient and family where they could not comfort and alleviate the child´s pain sufficiently:

> *"It feels difficult for the whole team. When it is a case like this, it feels distressing that you cannot ease the pain. When they are in so much pain, and you cannot help them, you cannot do it well enough… this feeling is difficult." N4*

The feeling of "not doing it well enough" was a source of considerable anxiety and distress for HCPs. They could feel the consequences of these feelings both physically and psychologically. However, no matter how distressed HCPs felt they still wanted to work as good professionals and collaborate with the families:

> "*Am I nervous to attend to the child because they would say unpleasant things to me? How do you go on being professional in these difficult situations? How can we all be professional together, so we can take care of these children? It may be that I'm sweating, but it's not me that's the problem, the child and parents are unhappy, I'm just the nurse, so how do we get it right together? It's our job to take care of everyone." N4*

HCPs also expressed concerns regarding making correct pain assessments and adequate opioid dosages as well as the fear of side-effects. Some nurses and doctors feared that morphine would affect children's respiration and they would stop breathing. This was mainly the case when they administered high doses of morphine:

> *"It feels unsafe when we give large doses of morphine. We never know when the child may stop breathing. I do not think that it is lack of knowledge, but it makes us feel insecure. Although the doctors are nearby, and we have permission to give the medicine. It still feels unsafe and unpleasant in a few difficult cases." N5*

However, HCPs also argued that if opioid dosages were administered correctly and the child's pain history was carefully considered, then the children would not stop breathing. Another concern surrounded the side effect of constipation, which was described as a common consequence of opioid administration and often a cause of abdominal pain:

> *"We must find the balance because the more we give morphine the more the child gets constipation and cramps. I think it's one of the most difficult things in my job because we do not know enough about it." D4*

Most nurses and doctors made a distinction between administering opioids to relieve physical pain and administering opioids to minimise anxiety and distress. HCPs explained their concerns when children specifically asked for intravenous morphine without showing signs of severe pain:

> *"I would prefer it given orally. But that does not provide the same sensation of feeling good. Intravenous morphine is quick in and quick out. Oral morphine helps for a much longer time. I try to explain that oral morphine helps for a longer time, but I cannot persuade them every time. So, when the children want to get intravenous morphine, I doubt sometimes this is the right thing to do." D1*

Older children could understand that morphine had an analgesic and relaxing effect. HCPs commented that even children 5-6 years of age could differentiate between oral and intravenous morphine and preferred intravenous morphine and requested it. The tendency to prefer the fast effects of intravenous morphine was further increased in older children and teenagers. Despite their concerns, HCPs emphasised that this was generally only a short-term problem. Children did not appear to become addicted in the long-term, it was only an issue when their illness was exacerbated. Nevertheless, opioids and their use in children was a challenging issue for HCPs and continuous education on pain topics was needed to diminish their concerns regarding correct pain assessment and adequate opioid dosages. Thus, clinicians' concerns and uncertainty were strongly linked to the subtheme of "getting pain assessment right".

Parental concerns regarding strong medication

Most parents had negative attitudes toward analgesics, especially opioids. Parental concerns for strong analgesics depended on the child's age and developmental level, especially parents with younger children were more afraid of morphine and its adverse effects. Parental concerns and attitudes toward opioids reflected their beliefs that opioids were related to addiction and they feared their child would become addicted. Parents associated addiction with severe psychological problems and a social stigma. Therefore, HCPs felt it was an important task to teach the parents and explain that sick children in general do not get addicted and would be off the medication when they got better:

> *"They think of their own fear of addiction and believe this would happen to their child. We must explain to them that sick children do not get addicted in the way they fear, and they will be morphine free when they get better." N1*

In this study, parental fear of addiction was most frequently observed early in the disease process. Several parents wanted to reduce the morphine doses as soon as the child's condition permitted it, while others held positive attitudes towards pain medication, as they had gained confidence in analgesics. These parents felt it was safe to administer morphine at home:

> *"When we are at home and she is in pain I call the hospital and I increase her morphine doses. I have it at home." P5*

Parents perceived that they were their child's main advocates and sought to play an active role in treatment decisions. They thought pain medication influenced the child´s condition and they worried that the drugs would increase the child´s fatigue. Furthermore, some parents were reluctant to use additional pain medication due to their belief that their child had already received more than an adequate amount of medication. For some parents, medication included drugs that aimed to cure leukaemia such as chemotherapy, steroids and antibiotics. On the other hand, medication used to alleviate symptoms should be avoided. Sometimes, parents preferred their child to tolerate pain or use non-pharmacological methods to relieve pain:

> *"Pain medication is good, but you must take care, it is like a bad circle … My wife and I think that medicine is good but used when it is only really needed and no more than that. It is better to be in a little in pain sometimes then being dizzy due to medication." P2*

Parents associated non-pharmacological interventions to a "normal" life whereas analgesics were considered "chemicals" and related to illness and undesirable side effects. It was challenging for parents to confront and accept that their child´s illness was profoundly serious when the child´s condition required strong pain medication. This increased their anxiety and fear of losing their child. In contrast, avoiding strong pain medication supported the feeling that their child was improving and would soon be cured. Furthermore, parents felt more comfortable when they used non-pharmacological pain relief. They listed a variety of non-pharmacological interventions: fresh air, heating pads, massage, hypnosis, playing with the child, exercise and different ways to distract their child, "everything but medicine". Generally, using non-pharmacological pain relief methods increased parental feelings of taking control and doing their best in contributing to their child's recovery.

> *"She only needed morphine for a short period of time. I think it is better for a little child to play than take a lot of medicine. She is very active, moves as much as possible. I play with her whenever possible and she rides a kind of bicycle. The staff believes that this is the reason why she does not have serious adverse effects after chemotherapy." P6*

4.6.2.3. Empowering families

This theme addresses the relationships, communication, collaboration and decision making between parents and HCPs, as well as coping mechanisms of parents and children in their handling of pain.

Relationship with families

This subtheme demonstrates that building a good relationship between HCPs and parents may enable an effective pain management.

There are many factors that contribute to the building or breaking of relationships between individuals and this is also true between families and health professionals. One clear characteristic that emerged from the interviews was that both families and HCPs depended on a good working relationship with each other to help the child. There are many types of relationships, including those that build on a more reciprocal relationship and those that are more one-sided. The latter is often the case between patients and HCPs. More cooperative types of relationships build on free communication between patients and HCPs. In this relationship, individuals feel free to explore their concerns and both parties contribute to a constructive dialogue. Individuals feel more at ease when they are treated in a friendly manner and the level of confidence between parties increases through time, because of good communication and trust. Consequently, HCPs acquire more information regarding the family history, while parents gradually understand more about their child's illness and their own role as parents. A common view for HCPs was the importance of establishing a collaborative relationship with families to effectively manage a child's pain relief. It helped HCPs to decide when it was good to talk about pain and to whom:

> *"On our ward, we spend more time talking with the parents than the children. This way, we can help them work together with us and help us interpret their child. An important part of my work is to obtain the trust of parents otherwise it is very difficult to work together … When the nurse informs me that the topic of the day is pain then I ask about pain. Sometimes this is good sometimes not. Because children do not always have the energy or interest to talk about it. It is like pain gets worse when they talk about it, so I must involve the parents, sometimes I take them out of their room so we can speak without the child." D1*

The relationship between HCPs and parents during a child's disease was like a teambuilding process where participants gradually got to know and trust each other. Therefore, parents preferred to collaborate with HCPs, who had a good knowledge of their child´s disease and family situation. Parents felt more confident when there was continuity and stability during the child's treatment pathway. Facing new staff and especially new situations, e. g. another department or hospitals felt distressing:

> *"Normally, I feel very safe. I notice at once when the nurse is new and lacks experience. It also feels unpleasant when there is a new doctor, who does not know my child´s history. P6"*

Decision making

An important goal of the HCPs' relationship with families was to empower the children and parents whenever possible. Patient empowerment relies on allowing patients to be involved in decisions regarding their own healthcare. When patients attain the appropriate knowledge, their empowerment enhances safety and the quality of healthcare. In this context, HCPs played an important role in helping families to understand leukaemia and to cope with the treatment program. As a result of a trusting therapeutic relationship, HCPs could empower children to be involved and to have some control of their own pain management, for example during a procedure when they were old enough to do so:

> *"Older children are widely involved in their assessments and decisions. I think we always succeed in working together with older children." D3*

HCPs empowered parents to play an active part in supporting their child during various activities including, among others, the administration of pain medication before painful activities for example brushing teeth when their child has severe mucositis:

> *"Most parents want to be involved in the child´s assessment and they want to help their children but some of them find it more difficult to get involved. It takes time." N2*

HCPs reported that each child and family had quite a different background and illness history and therefore different communication styles were needed. This coincided with parental need for individually tailored communication, e.g. when there was a change in disease stage status. In this

instance, both mothers and fathers often requested clear communication to facilitate continuous understanding and involvement, thus allowing the parents to achieve some sense of control.

> *"We said from the beginning that we wanted to be fully informed and to be involved in the treatment. You know, plan A we do this and if it doesn't work then we go to Plan B." P2*

Parents perceived themselves as having main caregiver responsibilities and wanted to be fully informed and involved in their child's treatment. This included monitoring their child's symptoms, advocating for their child´s care and helping their child through therapies regardless of the age of the child. Parents' comments regarding the HCPs emphasised that they listened to parental suggestions, including decisions regarding medication, and they acted together as a team devoted to alleviating their child's pain. Nevertheless, HCPs felt that responsibility for the overall treatment of the child ultimately lay with the clinicians as parents could feel "the burden".

> *"I explain to parents that I want to hear their opinion because they know the child's reactions. But I try not to make them feel the burden of responsibility for the treatment. "D2*

Child-parent coping

This is about helping families to build effective coping strategies. Parents reported that HCPs provided useful information, which helped them understand leukaemia and cope with it. Building coping strategies was a process, where parents relied on different parts of their background including personality, profession and parenting style. Mood and attitudes also influenced coping strategies. Identifying and focusing on the positive aspects of the experience made the disease a manageable reality:

> *"She was a beautiful girl with long hair now she has no hair and she has gained 15 kg, so she looks different. But she is still a happy girl and that means a lot to us. She has a hat, but she takes it off if it's too hot. I mean she accepts her disease. Hair loss and weight gain are parts of it. We are happy she copes with it. "P1*

Both parents and HCPs stressed that physical activity was an important pain relief method. Therefore, physically active children were more likely to maintain a sense of normality and the perception of their illness would improve over time:

> *"it must be something about the mindset and about limits, to try to push those limits. I remember one of them, he kept on trying to play badminton, it was particularly important to him. I think it was a form of pain relief. I mean try to get them off the bed to minimise their sickness identity. "D3*

Overall, the HCPs' relationship with parents played an important role in how children and parents coped with illness. In addition, this relationship was central to making decisions regarding pain management. Nevertheless, the relationship between HCPs and parents was often fragile and easily influenced by parents concerns and uncertainty. Therefore, the themes and subthemes are linked to each other throughout the interviews.

4.7. Summary

This chapter described the methods, ethical considerations and process of collecting and analysing data from 16 interviews with clinicians and parents of children with ALL. Using thematic analysis, three overarching themes were identified: complexity of pain assessment, anxiety and fear for the unknown and empowering families. The last section of this chapter is a description of the qualitative findings. The discussion of findings will follow in Chapter 5.

5. Chapter 5 Discussion of Study 1

5.1 Overview of Chapter 5

This chapter provides a discussion of Study 1, "Pain in childhood leukaemia: experiences of parents and clinicians", which was presented in Chapter 4. The first section discusses the interview findings. The last section addresses the strengths and limitations of this study.

5.2. Discussion of interview findings

By applying a thematic analysis of the interviews, three overall themes were identified to ease the interpretation and discussion of the results: complexity of pain assessment, anxiety and fear of the unknown and empowering families. The subthemes identified in the main themes (Table 4.2.) are discussed below in the next section.

5.2.1. Signs of pain

An essential component of any pain treatment is the ability to identify the pain, and the ability to identify if a pain treatment has the desired effect. In other words, the assessment of pain levels is pivotal. Pain assessment in children with ALL is particularly challenging, to which also several participants alluded. Fortunately, the interviews provided quite clear indications as to *why* pain assessments in children with ALL are as difficult as they are. In this context, HCPs addressed the fact that a child's pain expression is multifaceted and depends on the sensory, emotional, cognitive cultural and developmental background of the child, as well as the context of the pain (Finley et al., 2009; Gatchel et al., 2007). A child's expression and experience of pain is also based on the reception that the child receives from the people around him or her (Cohen et al., 2018). The expression of pain is decoded by the parent or clinician and their interpretation in a specific context is influenced by a multitude of cultural, social and institutional factors.

Parents used their child's behaviour to assess the level of pain the child was experiencing. These observations are consistent with previous studies (Bettle et al., 2018), and the approach seems reasonable for several reasons. Firstly, being a child, it comes naturally to express a physical condition honestly, directly and without evasion. The child's physical activity and social interaction were simple measures, which were also emphasised by the participants. Knowing the child in detail (parents) or having observed a child through longer time or many children over the years (HCPs)

would obviously increase trust in the assessments. Nevertheless, participants also raised some conflicting issues themselves. Some HCPs described that administrating painful chemotherapy to the child would automatically change their perception of the state of the child- now they were expecting a pain response, and so objectivity was compromised. However, when treating a child with the risk of inflicting pain, special attention to this pain seems reasonable. This is consistent with existing literature indicating that treatment-related pain is more problematic than disease-related pain (Ljungman et al., 2000).

The signs of pain in a child could, however, differ depending on a child's developmental stage. ALL is a chronic, painful and potentially deadly disease that seriously affects a child's life (e.g. difficulties in attending school and social events) (Eiser et al., 2017). Younger children may understand their condition to a lesser extent than adolescents and tend to adjust to it better. In contrast, adolescents can understand the implications of their disease and may experience a variety of thoughts and emotions. For example, they may desire to move beyond the cancer experience, or may become more reserved, depressed or anxious (Enskär, Carlsson, Golsäter, et al., 1997). Also, with older children and adolescents, communication inevitably becomes more verbal, which provides the advantages of revealing several aspects of pain. Furthermore, when the child understands the pain scoring, HCPs can involve the child in pain management decisions (Tsze et al., 2013).

HCPs described that older children more often reported severe pain. There is some evidence of higher levels of pain and distress in older children compared to younger children with leukaemia (Van Cleve et al., 2004). Moreover, older children with leukaemia were more likely to receive opioids during leukaemia treatment (Getz et al., 2018). However, these findings were questioned in another study that found no difference in symptom burdens associated with a child's age (Hedén et al., 2013). Research literature has demonstrated that the prevalence of chronic pain increases with age and peaks in adolescence (Roth-Isigkeit et al., 2005). Although this knowledge is obtained from children with non-malignant conditions, it seems reasonable to believe that chronic pain in leukaemia has some common features with other chronic pain conditions. In contrast, studies of acute procedure-related pain found higher ratings of pain and anxiety in younger children (Fradet et al., 1990). A parent's prediction of how upset the child would be before the procedure was a predictor of the observed distress and self-report of pain. Consistent with this idea, parents of

preschool children were more likely to report that their child experienced procedure- and treatment related pain and anxiety during ALL treatment (Dupuis et al., 2016).

5.2.2. Getting pain assessment right

HCPs' methods for pain assessment were based on available guidelines, which were found useful for most patients. However, more attention and knowledge were needed when large doses of opioids (i.e., larger than recommended by the guidelines or prescription labels) were used. These findings suggest that professional education in paediatric pain is an important element in providing effective pain management (Kavanagh & Watt-Watson, 2007). Nevertheless, HCPs described that they did not always use their knowledge in clinical practice. Thus, despite the awareness that using pain scales was important for optimal pain assessment and management (Bettle et al., 2018; Twycross, Parker, et al., 2015), these scales were infrequently utilised by HCPs (especially by doctors) (Moutte et al., 2015). Furthermore, parents seldom used pain scales as they considered knowledge of their child was sufficient to assess their child's pain (Linder & Wawrzynski, 2018). However, the literature indicates that teaching parents to use a pain assessment instrument may impact on their knowledge and attitudes toward pain medication (Huth et al., 2003).

Another important aspect described by HCPs was that a good knowledge of the child and family was required to correctly assess child´s symptoms. Therefore, HCPs needed time to listen to the child and family and to document the assessment and management of pain. Consideration of a high workload and insufficient time for patient related tasks was highlighted as a barrier to providing optimal pain treatment (Burston & Tuckett, 2013).

5.2.3. Pain as a mask

HCPs and parents perceived emotional distress associated with ALL related pain differently, with HCPs referring to this condition as "pain due to psychological distress". Such pain seems to cover a complex sum of psychosocial factors (e.g., the child´s developmental status as well as past pain and anxiety experiences) and parental understanding and coping with the child's disease. Consistent with previous studies, HCPs described that psychosocial components were found to have a major influence on a child´s pain experience (Hedén et al., 2013). According to HCPs, most children experienced a certain level of pain, anxiety and distress (e.g. due to living with a chronic life-threatening disease) (Dupuis et al., 2016). However, children who have already experienced

physical pain and anxiety would be prone to experience higher pain levels at subsequent similar procedures. This indicated that children's memories played an important and reinforcing role in their experience of distress (Chen et al., 2000). Although differentiating between anxiety and pain was a key challenge, HCPs emphasised that managing a child's pain and anxiety was mandatory to prevent an increased pain response in the future (Dupuis et al., 2016). Additionally, complex past pain experiences might require HCPs to individually tailor pain relief strategies and provide a detailed documentation of a child's (and parents') experiences in their medical records.

5.2.4. Clinicians concerns and uncertainty

High levels of "pain due to psychological distress" were mainly attributed to parental anxiety by HCPs. Consistent with previous research, parental anxiety played a significant role in parental perception of a child´s pain and quality of life (Link & Fortier, 2016). Parental catastrophic thinking about pain was associated with increased ratings of a child's pain (Langer et al., 2009; Quartana et al., 2009). In addition, parental solicitous behaviours were associated with higher functional impairment among children with greater psychological distress (Peterson & Palermo, 2004).

The clinicians who participated in this study were experienced nurses and doctors, who have been working in the clinical setting for 21 years (in average) and with child cancer for at least five years. However, HCPs expressed concerns regarding parental anxiety and the way anxious parents influenced their child´s pain experience and management. Children who expressed higher pain and requested more analgesics than HCPs considered they needed, required a greater level of attention and resources for care. Interpreting discrepancies between stated and observed or measured behaviours can be challenging (Linder & Wawrzynski, 2018). The issue could be that pain due to psychological distress could present as physical pain e.g., stomach pain or headache. It would be wrong not to treat this symptom, but the administration of analgesic medication does not remove the psychosocial component of pain (which according to HCPs, was strongly associated to parental anxiety and solicitous behaviour). On the other hand, pain could be a warning signal for complications to ALL treatment, e.g., infections, thrombosis or pancreatitis (Toft et al., 2018). Furthermore, some children tend to develop a rapid tolerance to opioids due to genetic characteristics and need larger doses of opioids to obtain pain relief (Sadhasivam et al., 2014). In this context, HCPs described the fear of "not doing enough" when they had a difficult patient and could not comfort and alleviate a child´s pain sufficiently. This fear was common for HCPs in both the paediatric ward and PICU, although clinicians in PICU were used to manage high doses of

opioids and sedatives as well as provide respiratory support (e.g., mechanical ventilation). Yet, clinicians' concerns about pain medication were related to the correct estimation of the causes of pain and adequate dosages of opioids. There was no difference between nurses' and doctors' approaches to opioids. Therefore, all of them highlighted that the administration of high dosages of opioids required great attention due to their adverse effects such as respiratory problems, depression and constipation (Getz et al., 2018).

5.2.5. Parental concerns about strong medication

A child's pain and pain management had considerable psychological implications for parents. Both parents and HCPs reported differences in how parents approached medicines, with some parents preferring not to give them. In accordance with other studies, parents held deep-seated concerns regarding the adverse effects and symbolism of opioids (Rony et al., 2010). One of these concerns was the parental fear of addiction, which was described by HCPs as a barrier for a child´s pain management. The reason for considering this fear as a barrier is that patients' beliefs and concerns towards pain medication are associated with adherence patterns and outcome parameters (Horne & Weinman, 1999; Timmerman et al., 2019).

The findings in Study 1 indicate that parental fear of addiction was strongest in the early stages of the disease. This concern seemed to diminish as parents learned more about their child´s disease (Earle et al., 2007). However, throughout the course of the disease, parents associated the use of morphine with a more severe illness and wished to reduce its use as soon as their child's condition permitted it. Cancer pain has been outlined as a referent for disease status leading to an existential meaning, while a prescription of morphine becomes a metaphor for impending death (Flemming, 2010). In this respect, parents were calling for more support from HCPs to help them manage their child's pain with non-pharmacological pain relief methods and as few analgesics as possible. This reinforced the feeling that the child's condition was somehow stable. In addition, supporting parents' role in alleviating their child's symptoms enhanced the feeling of normality, which parents quite understandably aimed for (Earle et al., 2007).

5.2.6. Relationship with families

HCPs described the collaboration with parents as teamwork and that it took time to develop such relationships. In agreement with previous research, a trusting relationship between HCPs and

parents ensured effective communication and helped families navigate through the experience of ALL (Bettle et al., 2018).

The findings in the current study exemplified, however, that the relationship to HCPs was fragile, that it could rapidly worsen if complications occurred or if a high turnover of staff took place. Parental distress influenced collaboration with HCPs, who felt that the relationship could turn into a struggle when parental anxiety and family conflicts generated unmet expectations (Burston & Tuckett, 2013). Although HCPs encouraged and empowered parents to manage their child, they emphasised that the responsibility for treatment was with the clinicians and protected the parents from this "burden". The parents, on the other hand, perceived themselves as having the main caregiver responsibility and wanted to be fully informed and involved in the child's treatment (Rodgers et al., 2016). In agreement with existing research, this finding indicates that parents preferred gaining information through clear communication and considering choices and options (Ljungman et al., 2003). All parents acknowledged having worries, and emphasised the fear of losing their child, but they had limited focus on the emotional aspects of the experience, preferring concrete information rather than emotional support (Pyke-Grimm et al., 2007). However, the emotional state of the parents determines their ability to hear and comprehend the information given (Eden et al., 1994). Therefore, enhanced communication is needed to meet the information needs of families (Levine et al., 2019).

5.2.7. Decision-making

HCPs highlighted the role of partnering with families and seeking children´s and parents´ perspectives in decision-making. In this context, HCPs emphasised two elements. Firstly, the individual child´s ability to communicate and cooperate during procedures (Cheng et al., 2019) and secondly, the nature of relationships between HCPs and their patients (Bettle et al., 2018). Approaches based on patients' personal preferences and behaviours when planning interventions were most likely to increase both children's and parents' confidence in treatment (Linder & Wawrzynski, 2018). Children´s active participation in decision-making was important for their experience of illness and treatment and subsequently for future experiences (Quaye et al., 2019). However, participants described that agreement in decision-making was variable. For example, it was challenging for HCPs to engage children in active participation when there were discrepancies between the families' and the clinicians' understanding of the situation (Linder & Wawrzynski, 2018).

5.2.8. Child-parent coping

While previous research has focused mainly on the maternal role and influence, more recent studies have also included the father's role as a care giver (Hill et al., 2009; McGrath & Chesler, 2004a). The present research found no differences between mothers' and fathers' perception of their child's pain. Furthermore, there were no indications of gender differences in how parents wished to be informed and involved in their child's treatment.

Parents generally expressed a preference for actively engaging themselves in daily functions and treatment decisions, aiming to bring a sense of normality during intensive treatment (McGrath & Chesler, 2004a). They tried to identify the positive aspects of the experience, focus on the future and help their child cope with the disease (Polizzi et al., 2015). Both parents and HCPs emphasised that a child's level of activity and mood influenced the coping response. Therefore, high post-diagnosis distress seemed to progressively decrease during the course of the disease and the children adapted to treatment related difficulties (Myers et al., 2014; Polizzi et al., 2015).

5.3. Strengths and limitations

5.3.1. Strengths

A strength of Study 1 is that it deliberately concentrated on the diversity of participants, who provided different perspectives regarding pain in children with ALL (Wu Suen et al., 2014). Therefore, clinicians were both nurses and doctors (consultants) in the paediatric oncology department or PICU, with an equal distribution of nurses and doctors from the two departments. Previous studies have mainly focused on nurses' experiences with paediatric patients (Bettle et al., 2018; Linder & Wawrzynski, 2018) and to a lesser extent on doctors' experiences (Levine et al., 2019). Furthermore, this study included clinicians from different medical specialties (paediatric oncology and intensive care). Enabling insight into various professional perspectives expands the existing knowledge about a child's experience of pain during the course of ALL.
An important aspect is that all HCPs were experienced nurses and doctors with considerable knowledge of childhood ALL. Clinicians' professional skills and ability to communicate to patients and families have been reported as developing over time (MacKay & Gregory, 2011). Such experienced HCPs could relate to different relevant situations and provide credible descriptions of challenges in pain estimation and management (Linder & Wawrzynski, 2018).

Another strength of this study is the inclusion of an equal number of mothers and fathers to reflect possible differences in female versus male parental perceptions. The present study found no differences between mothers' and fathers' perspectives on their child's pain. Both genders described similar concerns and wanted to be informed and involved in their child's treatment. Previous paediatric research has mainly focused on maternal roles and influences on children with leukaemia (Earle et al., 2007). Other studies have targeted both parents, but maternal participation was dominant (Bettle et al., 2018). Although some research suggests that fathers want to engage themselves in childcare and treatment decisions (Hill et al., 2009; McGrath & Chesler, 2004a), there is a paucity of research that focuses equally on mothers and fathers of children with severe conditions (Phares et al., 2005). This study therefore contributes to new knowledge in this area.

5.3.2. Limitations

The intention of this study was to include the same number of participants in every category (in this case three participants). However, the number of consultants working with children with ALL was limited so only two paediatricians and two anaesthetists were included. The adequacy of the final sample size was evaluated during the research process (Malterud et al., 2016). The transcripts were continuously reviewed and data collected was found to be relatively homogeneous for HCPs and parents, respectively. Therefore, the researcher considered that no new ideas would emerge from conducting several interviews (Francis et al., 2010).

5.4. Summary

This chapter discussed the findings of Study 1, that used a qualitative approach to exploring the experience of parents and clinicians in a child's pain in ALL. Getting pain assessment right is a challenging process that involves different tools, such as guidelines, pain scales and the experience of HCPs in contrast to "knowledge of my child" applied by parents. According to HCPs, older children and adolescents experienced more pain than the younger children with ALL. HCPs and parents perceived emotional distress differently, when associated with ALL related pain. In this respect, HCPs emphasised that psychosocial components played an important role in a child's pain experience. The findings in the current study suggest that in ALL, parental anxiety has a major influence on a child's pain ratings, solicitous behaviour and coping. Furthermore, parental anxiety may challenge HCPs' professional identities and workload. HCPs concerns referred to best pain management practice and highlighted undertreatment with analgesic medication. This contrasted

with parental wishes to avoid opioids whenever possible. Finally, this study found no differences in mothers' and fathers' perspectives on a child's pain in ALL.

6. Chapter 6 Study 2: Pain variations and management in childhood acute lymphoblastic leukaemia

6.1. Overview of Chapter 6

This chapter provides a review of Study 2: "Pain variations and management in childhood acute lymphoblastic leukaemia". The first section outlines the methods of this study. The following section addresses research ethical considerations. Finally, the results of the study are reviewed.

6.2. Methods

In this study, a quantitative approach was used to investigate a child's pain experience in ALL.

6.2.1. Participants

In Denmark, children with ALL are treated at four tertiary hospitals placed in four different cities: Copenhagen, Aarhus, Odense and Aalborg. The idea of studying children's self-reported pain in ALL emerged during scientific meetings with paediatricians from the Nordic and Baltic countries. Their expert opinion provided feedback during the development of a mobile application, which is the first paediatric pain app in this geographical area.

A consecutive sampling method was used to ensure equal opportunities for participation, therefore aiming for a good representation of the overall population within a reasonable time frame. The target of potential participants was set after gaining approval from the Central Denmark Region Committee in Biomedical and Research Ethics in March 2018. It was estimated that data collection had to be completed by the end of 2019 to ensure that this research study was finished in time, meaning that the inclusion of new participants would last 1.5 years. In Denmark, approximately 30 children and adolescents below 18 years are diagnosed with ALL annually (Hjalgrim et al., 2003). Thus, approximately 45 children were expected to be diagnosed during 1.5 years of inclusion. However, some children were expected to be excluded according to the inclusion/exclusion criteria described below. For example, children with chronic pain conditions like juvenile arthritis were not considered eligible, as their past pain experience could influence their experience of symptoms during ALL (approximately 100 Danish children and adolescents under the age of 18 years are diagnosed annually with juvenile arthritis) (Herlin, 2008). In addition, children with developmental

delay (e.g., due to different genetic conditions), were not considered eligible due to various challenges faced by these patients and their families. Notably, some of these genetic conditions have an increased risk of developing ALL (about 2% to 3% cases of childhood ALL occur in children with Down syndrome) (Whitlock, 2006). The number of potential participants was discussed with the supervisors and the paediatric consultants responsible for the ALL treatment at the four tertiary hospitals. Although it was not possible to predict the number of children that might meet the inclusion criteria, the result of these discussions was that approximately thirty children were expected to be eligible during the study period.

The researcher assumed that the eligible patients would be informed about this study and might consider participation. It is desirable to include as many eligible participants as possible, as a large sample size supports the generalisation of findings to a larger population. However, the recruitment of children in research studies is challenging. Although children might be eligible, they might be less willing to participate in research. For example, younger children and their families, who have less disease experience, are less willing to participate in clinical research due to time constraint and the extra burden of research (Hein et al., 2015). This is an important aspect in leukaemia research as the incidence of ALL is highest in children younger than five years (Clarke et al., 2016). Moreover, children with ALL are involved in several research projects regarding treatment protocols (Heyman et al., 2018) and the children and their families experience a high level of distress during the disease pathway (Sawyer et al., 2000) that may diminish their willingness to participate in research (Colville, 2012). The issue of drop-out was also discussed, as drop-out rates in paediatric research are often quite high, ranging between 7-35%. One of the risk factors associated with high drop-out rates was a long surveillance time in longitudinal studies (Sindhu et al., 2019).

Inclusion criteria:

Children aged 1-17 years with newly diagnosed ALL admitted to the participant paediatric oncology departments were invited to participate in the study. Participants were included within a week from the date when treatment commenced or soon after. Parents received written information (Appendix 7). School age children received an information sheet written especially for them to facilitate their understanding and cooperation (Appendix 8). Interpreters were available at the Danish paediatric oncology departments for non-speaking Danish families.

Exclusion criteria:

Children with chronic illness associated with pain (e.g., juvenile arthritis).
Children with developmental delay (motor or cognitive delay for which children receive support).
Families who could not cope with the burden of research in this study (e.g., parents with mental health issues).
Participants included later than three months from the start of treatment.

In the current study, children older than 10 years provided self-reports while pain in children younger than 10 was reported by their mothers. One advantage of investigating a child's pain from a parental perspective as opposed to a child's perspective, is that reports for every child can potentially be provided, including those who cannot respond for themselves (Cheng et al., 2019). Moreover, the use of the same instrument regardless of the child's age may facilitate data collection in rare conditions (Hedén et al., 2013). Previous research demonstrates that using parental reports alone or combined self-reports of older children with parental reports of younger children, are effective ways to collect data in paediatric populations with different developmental stages. Therefore, Dupuis et al (2016) asked parents of children aged two to 10 years to report children's pain and anxiety at one, six and twelve months after diagnosis of ALL. This approach was also used by Hockenberry et al (2017), who collected data on symptom trajectories from children aged three to 18 years old at four points during the first 18 months of ALL treatment. Parents completed symptom assessments for younger children, whereas children seven years and older provided self-reports.

Recruitment strategy

Prior to data collection, the researcher met key members of the clinical teams (nurses and doctors) to present the project. Staff at the paediatric oncology departments were informed during workshops about pain and a short film about reporting pain data in the app was included in the presentation. Furthermore, written information was available in the wards and was sent to all staff members via email. Recruitment took place during daytime working hours.

Within the research process, local nurses acted as gatekeepers to families of children with ALL and played a key role in ensuring that the researcher gained access to potential participants at four hospitals. The use of gatekeepers was required as the researcher had limited access to a vulnerable

population that was treated at a variety of Danish hospitals, which were geographically dispersed hundreds of kilometres from each other. Moreover, the gatekeepers knew the patients because they worked at these paediatric oncology wards and were able to approach potential participants at times when recruitment may have incurred minimal distress (Linder & Wawrzynski, 2018). This strategy was a safety mechanism designed to reduce distress and overcome a potential ethical barrier (the researcher was not a part of the local staff). The positive influences of gatekeepers can be invaluable to the research process to facilitate recruitment and minimise participant distress. However, at times, the use of gatekeepers can be problematic due to understanding about the research, communication issues, motivation issues or anxiety about the outcome (McFayden & Rankin, 2016). The researcher sought to keep the gatekeepers motivated by sharing a clear information about the project before start and keeping them updated during the process of research. Discussions and meetings with the gatekeepers were held every second month. At these occasions, the researcher reviewed the recruitment procedures and project details including the use of the app. Parents and children with ALL were assessed for eligibility with the help of these local gatekeepers, who asked potential participants whether they were happy to be approached by the researcher. Potential participants who indicated they were happy to be approached were provided with written and verbal information by the researcher (Appendix 7 and 8). Next day, after obtaining written consent from parents (Appendix 9) and assent from older children, the researcher provided an additional opportunity to ask questions and instructed the participants in completing the app. The researcher was available for further questions throughout the study period.

6.2.2. Data collection tool

As background work to develop the pain related items about leukaemia, the researcher undertook two studies. The first study, a survey based on a specially designed questionnaire identified the pain management strategies used in childhood leukaemia in the Nordic and Baltic countries (Jensen, 2015). This work demonstrated some institutional differences in the use of analgesics (e.g., different opioids) but similar challenges in the assessment and management of a child´s pain.

The second study focused on the prevalence of neuropathic pain in children with ALL and the results were presented at the 11th International Symposium on Paediatric Pain (Jensen, 2017). In this study, data on pain scores, functional symptoms and analgesic management were extracted retrospectively from the medical records of 35 children with ALL aged 1-18 years treated at Aarhus University Hospital between April 2012 and August 2014. Neuropathic pain diagnosis was

established when at least three of five criteria were present: administration of vincristine, pain scores greater than five on FLACC or NRS 0-10 scales during opioid medication**,** mucositis**,** functional impairment and the use of adjuvant analgesics (the pain scales are presented in section 2.9). The results of this study suggested that neuropathic pain was common in ALL but age-related factors were challenging in establishing the diagnosis of neuropathic pain, which was only established in children older than five years. Paracetamol, morphine and antidepressants were the main drugs used for pain relief. However, data collected retrospectively generated several uncertainties. Pain scores greater than five on FLACC or NRS scales in more than 50% of observations might have reflected that clinicians recorded high pain scores to document the need of pain relief interventions while pain free episodes were less frequently documented. Furthermore, data on the frequency of pain and efficacy of pain relief strategies were rare and inconsistent. Moreover, pain and symptom severity and the use of pain medication recollected by outpatients were probably less accurate than during hospitalisation due to recall bias.

The findings of these two studies and the aim of this doctoral research were presented at NOPHO scientific meetings, where discussions with paediatricians identified the need of a prospective, longitudinal exploration of pain reported by children or their parents during the first months of ALL treatment. Focusing on pain reported by children or their parents aimed to reflect the wide age-range of childhood ALL (1-18 years), who were treated both in-hospital and at home as previously reported by Van Cleve et al. (2004). Self-reporting has been often emphasised as "the gold standard" in the assessment of paediatric pain (Turk & Melzack, 2011). Although children as young as five years of age are able to report their pain, the voice of children can be compromised by their illness and developmental stage (von Baeyer, 2006). Parents can provide additional information to support their children or act as proxy reporters when obtaining reports directly from the child is not possible (Cheng et al., 2018). The concordance between children and parents' pain reports has been described as good or moderate in some studies (Baggott et al., 2014; Zernikow et al., 2005) while others have reported less concordance (Zhukovsky et al., 2015).

Self-reporting in paper-based approaches has been commonly used in pain assessments (Collins et al., 2000). However, patient recall of past experiences can lead to inaccuracies in the reporting of symptoms as pain reports can be influenced by a patient's current state of pain and emotions. Moreover, patients may adopt a back filling approach or they complete the paper-based diaries just prior to returning them to the researchers (Stinson et al., 2013).

The researcher chose the use of a mobile application for data collection in this quantitative study because these applications were accessible on smartphones and tablets and patients could report their symptoms in the moment rather than having to remember them later (Wesley & Fizur, 2015). The use of electronic pain assessment was tested and found applicable in adolescents with cancer (Baggott et al., 2012; Stinson et al., 2013) (section 2.9.3) but there was no app in the Danish language, providing a clear gap for Danish children and young people with ALL.
The mobile application in this study, the How-R-you app serves as a mean to empower patients to keep track of their daily symptoms and was envisioned as a supplement and potentially a substitute for more traditional tools of collecting health data (e.g., paper questionnaires). The app is the result of a collaboration between the researcher, the Department of Paediatrics and Adolescent Medicine at Aarhus University Hospital, the Business Academy Aarhus and Aarhus University. The online platform is a web-based software that was developed by a software engineer from the Business Academy Aarhus, Denmark. The app contains modularised and configurable health related questions. These questions were designed by the researcher in collaboration with paediatricians according to recommendations from the International Association of Study of Pain for the core outcome domains and measures that should be considered in clinical trials of treatments for acute and chronic pain in children and adolescents, such as pain intensity and physical and emotional functioning (IASP, 2019).

Moreover, the protocol of Study 2 was reviewed by the NOPHO Scientific Board. Thus, expert opinion of paediatric oncologists from the Nordic and Baltic countries was used to provide feedback on the relevance for clinical practice in childhood leukaemia. The result of this cooperation is the first app in the Nordic countries that enables a continually self-monitoring of pain and its impact on physical and emotional functioning of children and adolescents with leukaemia. The app has been further developed and used in other projects regarding children with juvenile arthritis (Müller et al., 2019). The How-R-you app is available for free on Apple and android devices and can be accessed on http://www.leukemia.sundata.dk.

Data was collected and stored in a secure manner in a central database at Aarhus University. Data could only be accesses with a personal login by the researcher. Technical data for the mobile application is documented on https://www.leukemia.sundata.dk/swagger/index.html.

6.2.3. Pilot test

The researcher tested the pain diary in a pilot study at the paediatric oncology ward, Aarhus University Hospital during September - November 2016. To test question clarity and acceptability as well as completion time (Rattray & Jones, 2007), a paper version of a pain diary was conducted prior to obtaining the final version of the app. A paper version was chosen due to practical reasons as its development did not require comprehensive resources. However, all participants commented that they expected a pain diary on a mobile application to be easier to complete than a paper version. Recruitment for this pilot stage followed those of the main study (described under "Recruitment" section). Three families (three children aged 12-16 years supported by one of their parents) completed a pain diary for one week. Their comments were collected and used to adjust the content and design of the pain diary. This resulted in the simple and uniform design of numerical rating scales (0-10) and a few changes, such as addition of mood score and pain score after pain medication and after non-pharmacological pain relief methods. In addition, the participants commented that the app seemed easy to complete for children older than 10 years who could read and understand the names of the analgesics (morphine, paracetamol, amitriptyline, nortriptyline and gabapentin). Although evidence supports the use of pain scales in children older than five years of age (McGrath et al., 1996; von Baeyer, 2006), patients' suggestions regarding children's maturity and reading abilities seemed realistic and were integrated in the final study design.

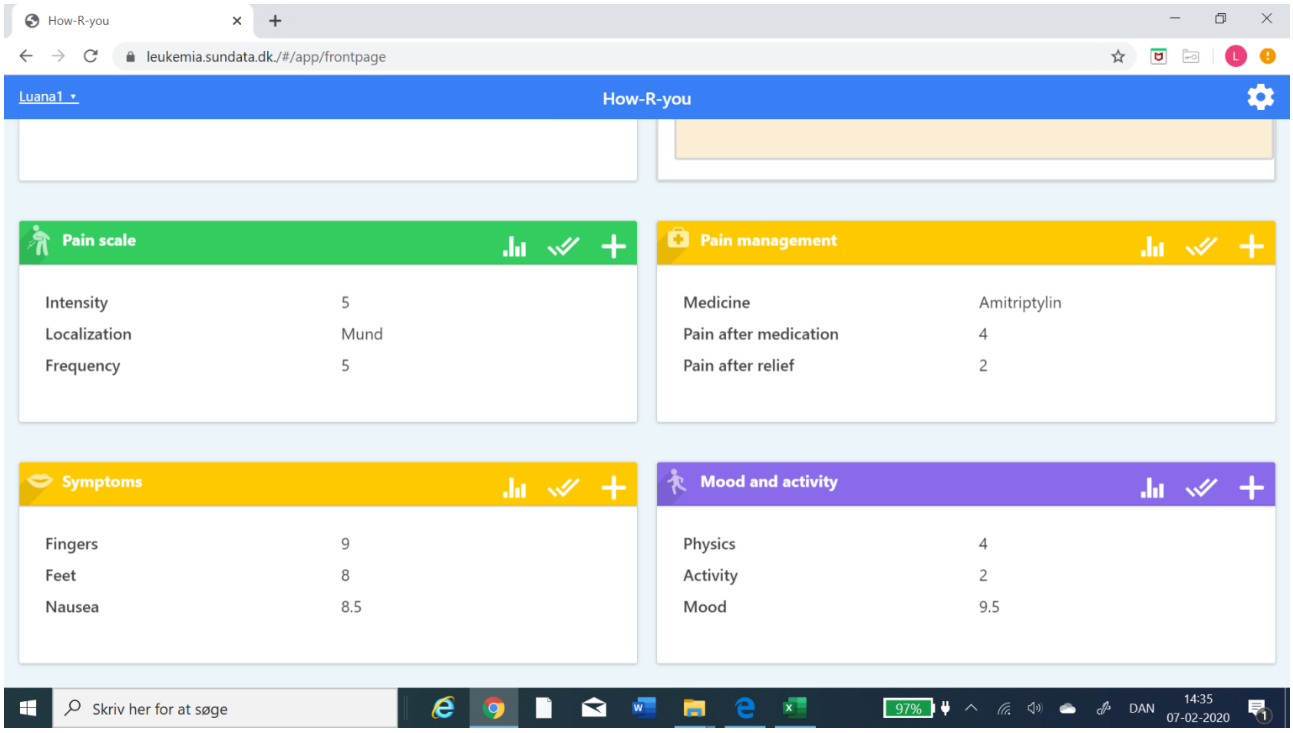
6.2.4. App description

The How-R-you app was designed as a symptom and medicine diary that could be used in several projects (with rating options adapted for juvenile arthritis or leukaemia). This study was conducted in Denmark where the individuals' first language is Danish, therefore this app was designed and completed in Danish. The app had seven parts: the first part was a calendar; the second part allowed participants to write different notes about blood samples or important appointments (optional). Chemotherapy could be recorded in the third part (optional). Pain intensity, location and frequency was recorded in the fourth part whilst pain management (medication and other pain relief methods) and the effect of these methods was recorded in the fifth part. Sensory disturbances (numbness) in arms and feet, muscle strength and digestive problems (nausea, constipation, mucositis) were recorded in the sixth part. The influence of pain on activity level and mood was recorded in the last part of the app. Overviews of previous registrations could be generated as graphs or tables.

Some parameters in the app could be rated 0-10 where 0 was “no” or “normal” and 10 was “worst” or “very much”. These parameters were: pain intensity, pain frequency, pain relief after medicine, pain relief after non-pharmacological pain relief methods, numbness fingers/feet, muscular strength arms/legs, nausea, constipation (stool), mucositis, physical activity: how active are you (e.g., play, run, write) general activity: does pain prevent you doing normal things? (e.g., being with friends) mood: does pain affect your mood?

The other parameters offered the possibility of choosing from among several options: localisation of pain (head, throat, mouth, chest, abdomen, back, legs, arms or anus) medicine (morphine, paracetamol, amitriptyline, nortriptyline, gabapentin or other) and non-pharmacological pain relief methods (heating pad, massage, distraction, other).

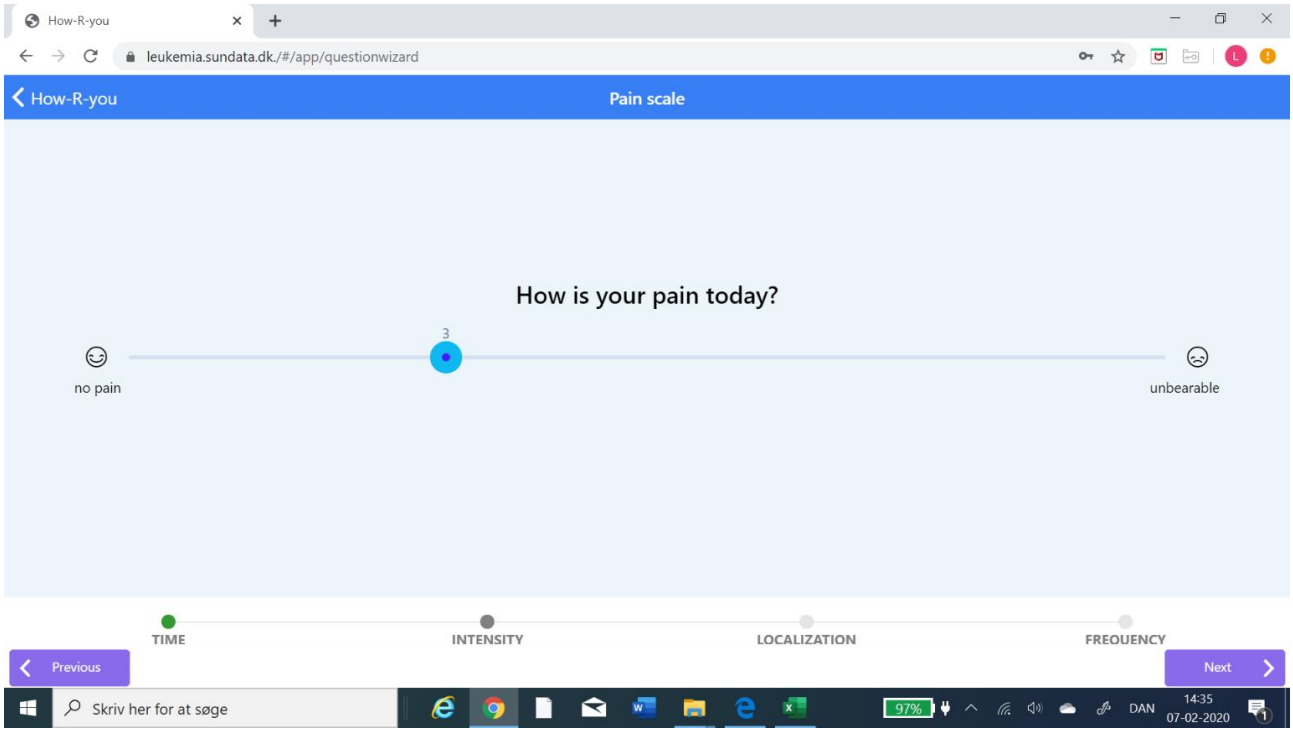
The app functions are visualised in the screenshots below. The first screenshot illustrates the rating options for the leukaemia app.



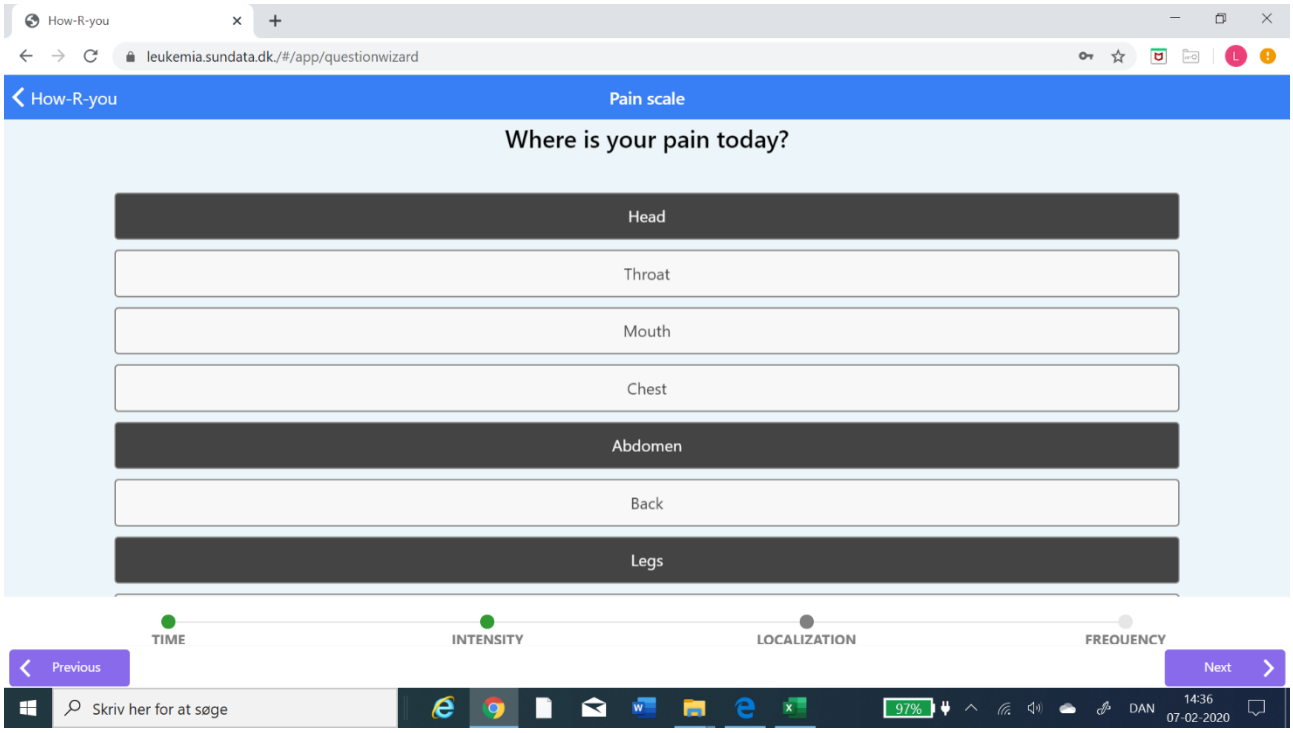
The How-R-you app is designed to be user-friendly and acceptable to those completing it. During the design process, the feedback from patients and doctors contributed to the selection of questions, their wording and response formats (e.g., slider scales, numerical input and multiple-choice answers). Therefore, questions are designed as touchable visual analogue slider scales from 0 to10 and the choices made on the screen are registered as numerical values. A digital VAS-scale can be

easily integrated into an electronic platform and provides a rapid universal access across different web interfaces. Recent research found no clinically relevant difference between paper-based assessment and VAS-scores obtained from digital VAS-scales completed on laptops or mobile applications (Delgado et al., 2018). In addition, the numerical registration of pain ratings was chosen to provide participants with a simple tool to monitor symptoms and response to treatment through overviews of previous registrations generated as graphs or tables. However, to ensure that the participants understood the scales, smiley faces were added at both ends of the scales (a happy smiley for "no pain" and a sad one for "worst pain") (Tomlinson et al., 2010). Technically, the simple design of the app did not support the use of other scales, such as a standardised pain rating scale for children (e.g., Faces Pain Scale Revised). Although the use of a faces scale could facilitate the pain scoring in children as young as five years old (von Baeyer, 2006) and is available in many languages including Danish, it was not included because these young children would not have been able to complete the other questions in the app that required reading and understanding abilities, therefore parental input would still have been required (section 6.2.3.). The choices made during the development of the app prioritised the simplicity and uniformity of scales with the purpose of facilitating the daily completion of the app and its clinical use. However, an implication of these choices was that in children younger than 10 years of age, the pain ratings reflected the parental perception of their child's pain, which is further discussed in section 7.2.5. In future work, whilst important to keep the design of the app simple for the reasons outlined, more powerful technology and software may enable greater sophistication in the app to align more closely with standardised pain rating scales and strengthen its use in research.

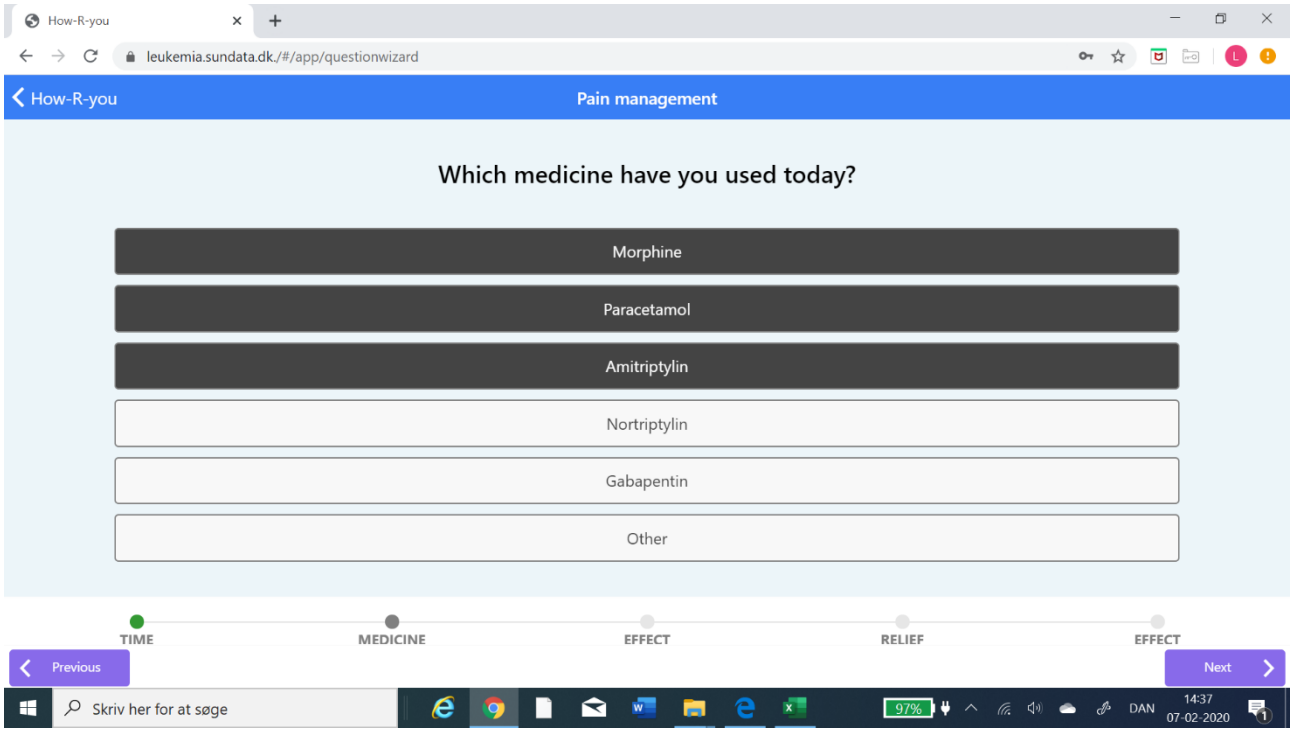
The screenshot below illustrates a pain intensity rating. Touching the "next" button leads to the next rating (e.g., pain intensity) on the screen.



The next screenshot illustrates pain localisation, which can be registered when chosen on the screen.



The next screenshot illustrates pain medication, which can be registered when chosen on the screen.



6.2.5. Procedure

After obtaining written consent, parents and children completed the app once daily for the duration of therapy for three months. The researcher instructed parents and children older than 10 years on how to score their symptoms and record medication. Children older than 10, who could self-complete the app, provided their own data. A minimum age of 10 years for self-reporting in the app was the researcher's choice based on previous approaches in paediatric oncology research and the results of the pilot test (Section 6.2.3.). For example, in a study about pain variations during cancer treatment, children older than 10 years answered by themselves while younger children were interviewed together with their parents (Ljungman et al., 1999). Von Bayer recommended the use of numerical rate scales in children older than eight years because although young children may be able to count, they have not yet developed an understanding of the quantitative significance of numbers (von Baeyer, 2006). Furthermore, the app registrations required reading and understanding abilities (e.g., the names of the analgesics) and a level of maturity to remember to complete the app daily.

Demographic data (a child's age, gender and time from diagnosis) and the person who completed the app registration (parent or child) were recorded in the inclusion of the study when the

participants received an ID code and created their own logon in the app. Identifiable data was not collected.

The app was completed during the first three months of the treatment, which corresponded to the induction and consolidation periods. Pain was recorded both in hospital and at home, as reported in most previous research (Van Cleve et al., 2004). However, this study did not collect information about the setting of pain recordings (home or hospital) and how this might have influenced the pain ratings.

6.2.6. Statistical analysis

Data collected in the app was exported to Excel and analysed using the statistical software package STATA 13. Descriptive statistics were used to describe the data separately on every participant. Based on the sample of participants in the study, the data was separated to compare the burden of pain in different age groups (children younger than ten compared to older children and teenagers). A Mann-Whitney U test was used to compare pain characteristics in two populations that may be not normally distributed, for instance due to the different number of participants and pain reports.

6.3. Ethical considerations

6.3.1. Ethical approval

The University Ethics Approval for this doctoral research was gained from the Research Ethics Committee for Health at the University of Bath (REACH) on the 13.10.2016 with reference EP 16/17 035.

For Study 2, approval was gained from the Central Denmark Region Committee in Biomedical and Research Ethics on the 19.03.2018 with reference 1-10-72-150-18 (Appendix 5). The study respects the Privacy Act and has received approval from the Data Protection Agency in the Central Region Denmark on 24.10.2016 with reference 1-16-02-579-16 (Appendix 6).

6.3.2. Ethical considerations in research in paediatric populations

There are ethical challenges that researchers face when they conduct research with children. According to Alderson and Morrow (2014), the ethics framework for conducting research in paediatric populations are duty, rights, harm and benefit. Therefore, the benefits of research as well

as potential risks, distress or adverse reactions related to research must be carefully considered. Furthermore, research is based on the conviction that children, just like adults, are citizens who hold their own views and perspectives. They have competencies, the right to be heard and can speak for themselves if the appropriate methods are used. Information, confidentiality, respect and consent from people with parental responsibility were central issues (Einarsdóttir, 2007).

6.3.3. Informed consent

Informed consent was obtained from parents (Appendix 7 and 9). In addition, children received written and verbal information according to their developmental level (Appendix 8) and gave their verbal assent (Health Research Authority, 2019). General issues on informed consent have been presented in Chapter 4, section 4.4.

6.3.4. Anonymity and confidentiality

Participants chose a username and login code, which ensured anonymous access and collection of data on the app. Names and unique personal identification data like date of birth were not entered on the app. The app can be accessed on http://www.leukemia.sundata.dk.
Participants were identified using an ID code assigned by the study. The ID code was linked to the patient ID in a separate document stored securely on a hard copy on another computer in a locked office. Data was collected in a secured central database at Aarhus University. Data could only be accessed with a personal login by the researcher. Technical data for the project is documented on https://www.leukemia.sundata.dk/swagger/index.html.

6.3.5. Risks, adverse reactions and disadvantages

This study did not influence the leukaemia treatment of participating children and caused no risk, adverse reactions or discomfort. Children with ALL undergo many therapeutic procedures and their parents hold many additional caring responsibilities, making their availability limited (Molinaro & Fletcher, 2018). Therefore, the app was designed to be easily completed (5-10 minutes daily). In addition, the researcher attempted to minimise any possible distress related to the questions and registrations in the app. Furthermore, coercion was avoided as the researcher was not a part of the medical team in the paediatric departments. The medical records of the participants were not accessed in this study.

6.4. Results of pain diaries

This section starts with a description of the participants. The following part addresses the results of the individual registrations. This is followed by an overview of data for all participants. Finally, details on pain registrations are highlighted.

6.4.1. Participants

Ten eligible participants were approached and invited to participate in this study between May 2018 and November 2019. Seven families accepted the invitation to participate, and the parents signed informed consent forms. The first child included in this study, a 12-year-old girl, sadly died a few weeks after inclusion. The parents could not remember the code to access child's data on the app, therefore their data was lost. Another nine families were approached at Aarhus University Hospital and six children were included. Two families did not wish to participate, providing reasons such as not wanting to think about their child's illness and treatment experience. Of the six participants who were included, one did not response to therapy and died shortly after inclusion.

Table 6.1. provides data regarding participants' pseudonyms, demographics and pain diary completion data.

Table 6.1.

Demographic data

Pseudonyms	Age (years)	Gender	Diary completed by	Time from diagnosis (days)	Participation time (days)	Number of diary days completed	Completion rate
Laura	5	F	Mother	10	93	83	89%
Victor	1.5	M	Mother	65	93	46	49%
Peter	16	M	Child	17	123	59	48%
Thomas	15	M	Child	8	11	4	36%
Lars	11	M	Child	9	93	57	61%
Rasmus	17	M	Child	5	93	60	64%

Note: F=Female, M=Male

Data in table 6.1. indicate that most children had been diagnosed for less than three weeks at the point of recruitment (mean=19, SD= 20.88, range 5-65 days). The mean age of the participants was 10.9 years (SD= 4.4, range 1.5-17). Therefore, a wide range of ages were represented: Laura and Victor were young (five and one and a half years respectively), and registrations in the app were

provided by their parents (mothers). The other participants were older (11-17 years) and provided their own registrations. The difference in children's ages might have generated differences in pain registrations. To investigate this difference, pain registrations from the group of young children (1-10 years old) will be compared to those of older children (10-17 years old) later in this chapter.

6.4.2. Results of individual registrations

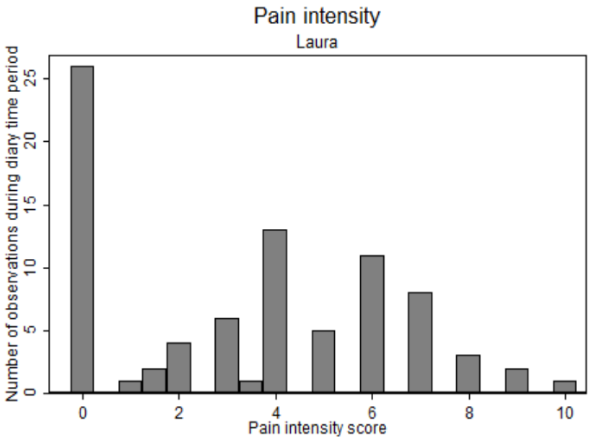
The individual registrations in the app (representing the daily ratings also called observations in the text), will be presented as histograms. Details for the structure of the histograms will be reviewed for participant 1 (Laura), while participants 2-6 will be addressed more succinctly.

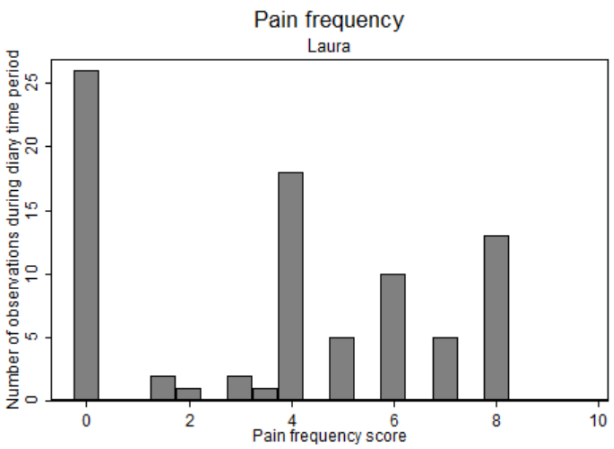
6.4.2.1. Laura

Laura was a 5-year-old girl, who participated in this study for 93 days. Of those 93 days, 10 did not contain any information, which corresponded to missing values. The missing values occurred around Christmas, New Years and a weekend. Laura has thus delivered 83 daily observations on each variable by using the app. That is the largest number of observations delivered among all studied patients.

Pain intensity and frequency

Of 83 observations, 26 consist of zero-values. In this context, zero-value means zero pain intensity and is not a missing value. Thus, Laura experienced no pain in 31.1% of the observations during the study period. The complete distribution of pain intensity and frequency values during the study period are illustrated in the histograms below.





The most frequent level of pain intensity experienced by Laura is “0”. Excluding the zero pain-intensity observations, the histogram of pain intensity for Laura shows what might resemble a normal distribution. When the zero-pain intensity observations are included, the histogram does not resemble a standard normal distribution, but a normal distribution with a large lower tail, meaning a large number of zero values. However, the low number of observations in the interval 4.9-5.9 demonstrate that even when the zero values scores are excluded, the pain intensity scores are only approximately normally distributed. The large number of zero pain intensity observations has a substantial effect on the mean value. The sample mean is 4.9 when the zero observations are excluded. This corresponds to an approximate normal distribution. However, when the zero values are included, the sample mean is 3.42. Although the median is close to the sample mean, the large lower tail of the distribution creates a lower sample mean compared to the median value.

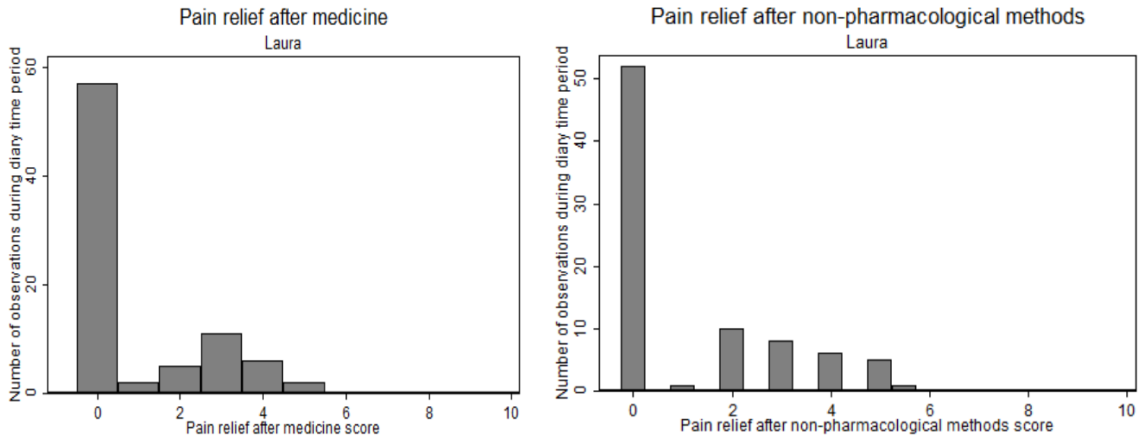
The relatively large sample standard deviation reflects that on average, any given observation of pain intensity deviates with 2.9 from the sample mean of 3.42. This further indicates that the distribution of pain intensity for Laura does not follow a standard normal distribution.

In accordance with the zero values for pain intensity, Laura experiences zero pain frequency when there is zero pain intensity. Thus, Laura experiences 26 days out of 83 with zero pain frequency, equal to 31.1% of the observations.

It is immediately noticeable that the histogram of pain intensity is different from pain frequency. The pain frequency experienced by Laura can be characterised as having several observations in both extremes of the distribution, as well as having a large number of observations in the middle. The sample mean is 3.74. The differences in sample mean between pain intensity and pain frequency can be explained by the larger upper tail of the pain frequency distribution, compared to pain intensity. The large tail of the pain frequency distribution indicates that pain frequency is not normally distributed. In this case, the 25% quantile is 0, the 50% quantile is 4 and the 75% quantile is 6. The sample mean for pain frequency is 3.74, which is only 0.26 points away from the median value. Although the median is close to the sample mean, the large lower- and upper- tail of the distribution clearly show that pain frequency for Laura is not normally distributed.

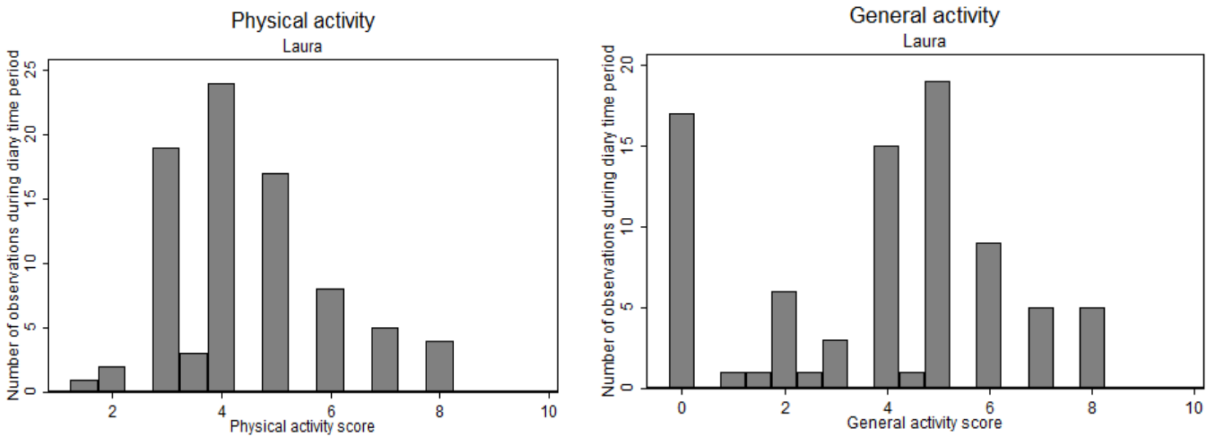
Pain relief

During this study, Laura has delivered 83 daily observations on each variable. The figures below illustrate Laura's pain intensity after receiving pain relief. The first figure shows that 57 (68.7%) observations regarding pain relief after medication comprise zero-values, which include 26 (31%) observations where Laura was pain-free without any pain relief and 31 (37%) observations where the ratings represented pain after receiving pain medication. Similarly, the second figure illustrates 52 (62%) observations comprising zero-values that include 26 (31%) ratings without any pain relief and 26 (31%) observations with non-pharmacological pain relief methods. The complete distributions of pain relief after pharmacological and non-pharmacological methods are illustrated in the histograms below.



Activity (Physical and General)

The complete distribution of physical and general activity during the study period are illustrated in the histograms below.

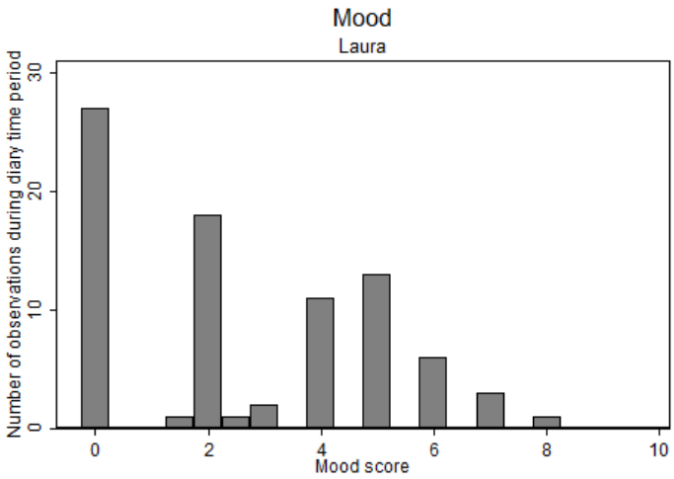


There are no zero values among the 83 observations, meaning that this participant did not experience normal physical activity at any time during the study period. The lowest value is 1.5 and the highest is 8 while the sample mean is calculated as 4.45. The distribution of physical activity looks like a normal distribution. The 25% quantile is 3, the 50% quantile is 4 and the 75% quantile is 5. The fact that the median is close to the sample mean values provides further evidence that physical activity is somewhat normally distributed. The sample standard deviation calculated as 1.45 also indicates that physical activity is normally distributed when compared to the histogram.

Of the 83 observations regarding general activity, 17 are zero-values, representing normal activity in 20% of the observations. The lowest value is 0 and the highest is 8 and the sample mean is calculated as 3.79. The distribution of general activity has a relatively large lower- tail. The difference in distribution between physical activity and general activity suggests that the two parameters are not necessarily correlated. Compared to physical activity, the lower sample mean from general activity is related to the large number of zero-values ratings. The sample standard deviation is calculated as 2.45. The larger sample standard deviation also indicates that the general activity deviates more from the sample mean as compared to physical activity.

Mood

The complete distribution of mood during the study period is illustrated in the histogram below.



Of the 83 observations, 27 are zero-values, which is equivalent to 32.5% of the observations. The lowest value is 0 and the highest is 8. The sample mean is calculated as 2.65. The distribution of

mood has a relatively large lower- tail and it is evident that more than half of the observations are lower than 2.5. Mood seems to correlate more with general activity than with physical activity.

Localisation of pain and other symptoms

Laura reported pain several places in the digestive system: abdomen (14%), throat (8%) and mouth (7%). She experienced moderate constipation in 15% of observations, nausea in 10% of observations and mucositis in 15 % of observations. Symptoms and pain in the digestive system are commonly related and, sometimes, difficult to differentiate. Nausea and mucositis were reported at the beginning of the study period, while constipation occurred throughout this period. Furthermore, Laura experienced headaches (15%) and pain in the legs (62%), which are often related to peripheral neuropathy. Muscle weakness in the arms was reported in 78% of observations, whereas diminished strength in the legs was more substantial and was present in all observations.

Pain management

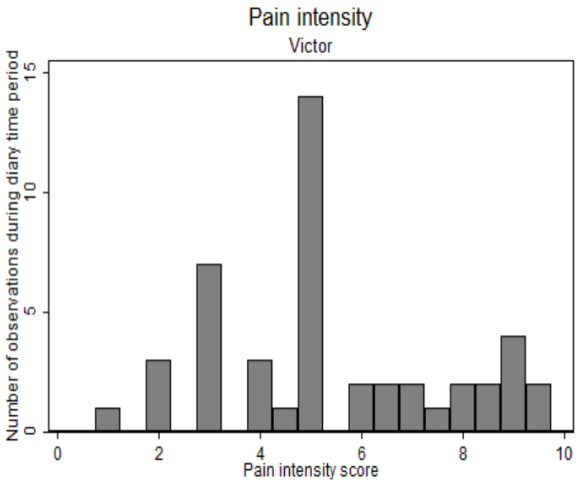
Paracetamol was the most utilised analgesic (59%), whilst morphine was only reported in 24% of observations. Massage and distraction were only used a few times (10% and 5% respectively).

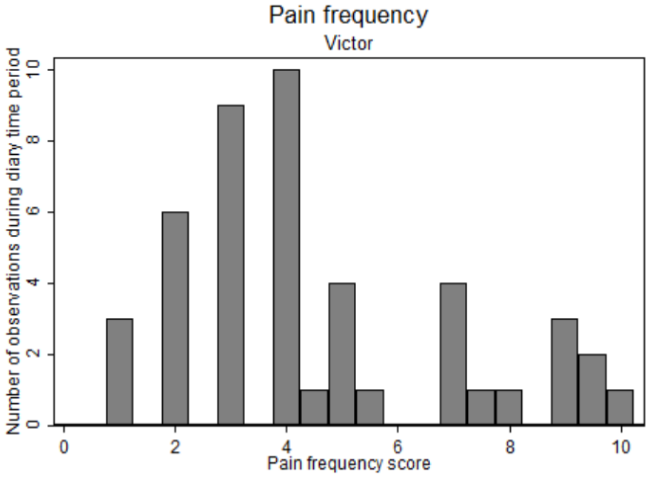
6.4.2.2. Participant 2 (Victor)

Victor was a 1.5-year-old boy, whose mother completed the app. He participated in the study for 93 days. Of those 93 days, 47 days (50.5%) did not contain any information, which corresponds to missing values. Victor has thus delivered 46 daily observations on each variable by using the app.

Pain intensity and frequency

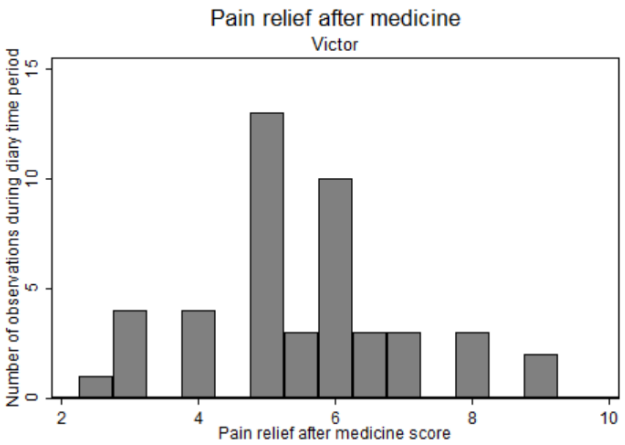
Victor reported the highest pain intensity among all participants, mean 5.41 (SD=2.3, range 2-9), being the only participant who reported no zero-pain intensity experience. In accordance with pain intensity ratings, there was no zero-value of pain frequency. Victor's pain frequency was in average 4.60 (SD= 2.5, range 1-10). The complete distribution of pain intensity and frequency are illustrated in the histograms below.

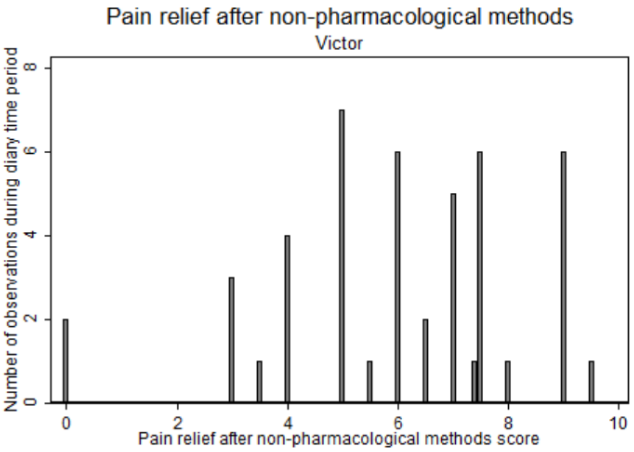




Pain relief

Victor did not seem to achieve effective pain relief with either analgesic medication or non-pharmacological pain relief methods (Table 6.5.). Therefore, there were no zero-values reflecting good pain relief after analgesic medication and only a few zero-values after non-pharmacological methods. The complete distribution of pain relief after medicine and after non-pharmacological pain relief methods are illustrated in the histograms below.

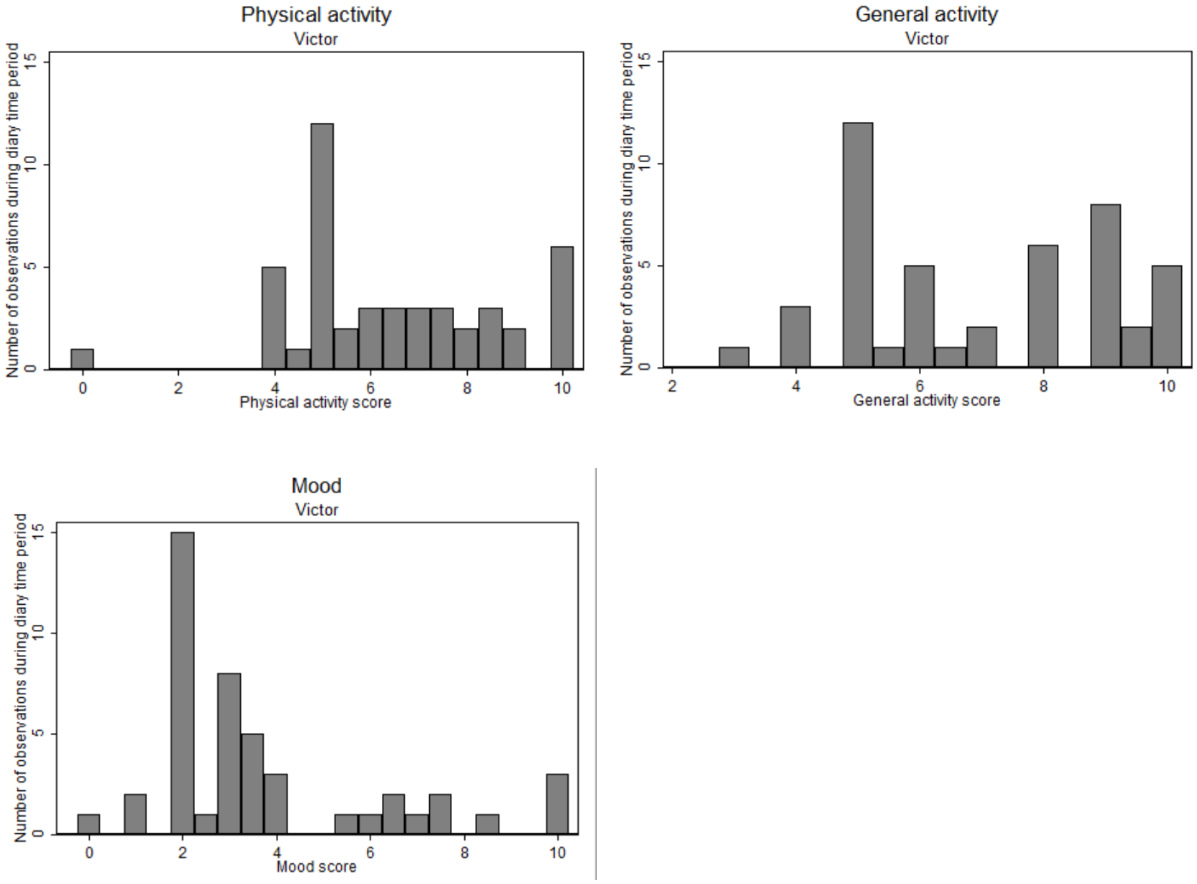




Activity (physical and general) and mood

Victor's mother reported that pain had a substantial impact on her child's physical activity. There was only one zero-value that indicated normal activity level at the beginning of the study period. Similarly, general activity was reduced and there were no zero-values supporting Victor´s substantial burden of disease. Although mood ratings were better than those describing activity

(mean= 3.76, SD=2.5), mood ranged widely from 0 to10. The complete distribution of physical activity, general activity and mood during the study period are illustrated in the histograms below.



Localisation of pain and other symptoms

Victor experienced frequent pain in the digestive system: mouth, abdomen and anus. He experienced sometimes intense nausea (reported in 32% of observations), ranging up to 9 on the 0-10 scale. In addition, a high level of mucositis, ranging 5.5-10, was reported in 26 % of observations. Both nausea and mucositis were mainly reported in the beginning of study period. Nevertheless, the most troublesome problem for Victor was pain in the legs, which was reported in 95% of observations. Moreover, substantial muscle weakness in the legs and numbness in the feet were reported in 100% of observations.

Pain management

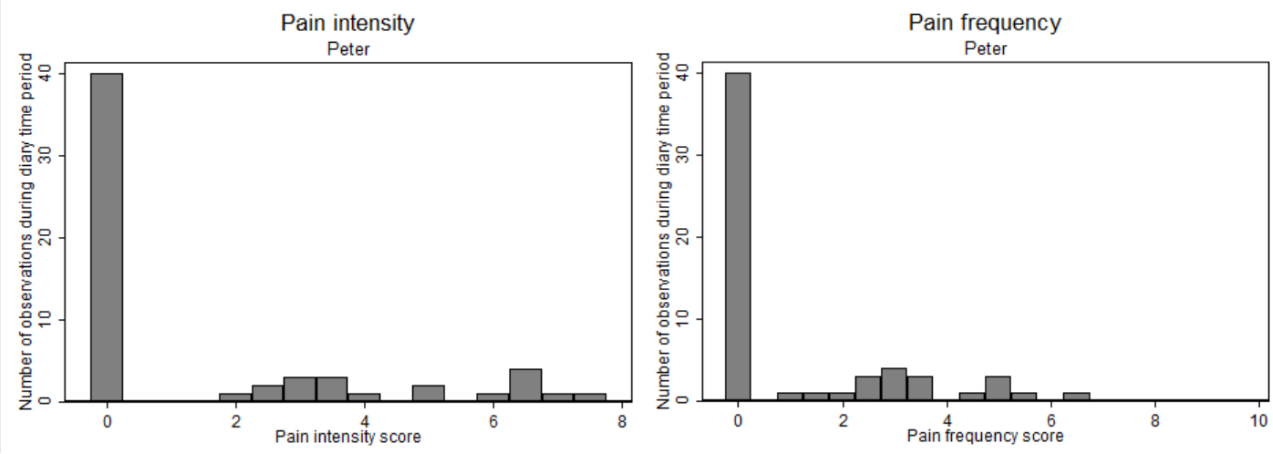
Paracetamol, amitriptyline and nortriptyline were used throughout the study period in 95% and 98% of observations respectively, whilst morphine was only reported in 15% (Table 6.7.) Distraction, in this case mainly iPad, was used daily as a non-pharmacological pain relief method.

6.4.2.3. Participant 3 (Peter)

Peter was a 16-year-old boy, who participated in this study for 123 days. Of these 123 days, 64 did not contain any information, which corresponded to missing values. The missing values occurred while Peter experienced severe complications. These problems required intensive treatment and multiple procedures, including several days admission to the PICU. When his condition became stable, Peter wanted to continue the app registrations. Peter has thus delivered 59 daily observations by using the app.

Pain intensity and frequency

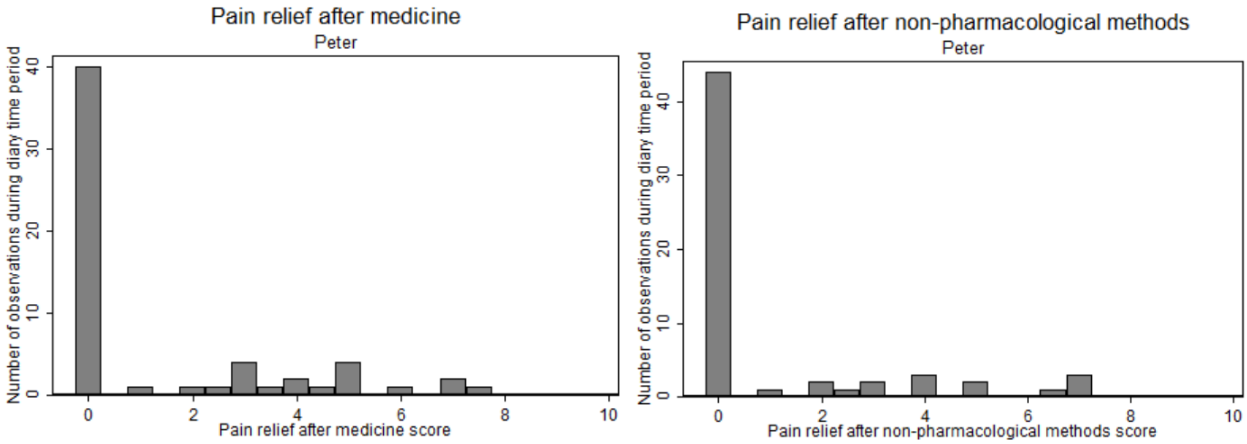
Of the 59 observations, 40 consisted of zero-values both for pain intensity and pain frequency, which was equivalent to 67.7% of the observations. It is immediately noticeable that in the histograms illustrated below the distributions of pain intensity and pain frequency were almost identical.



Pain relief

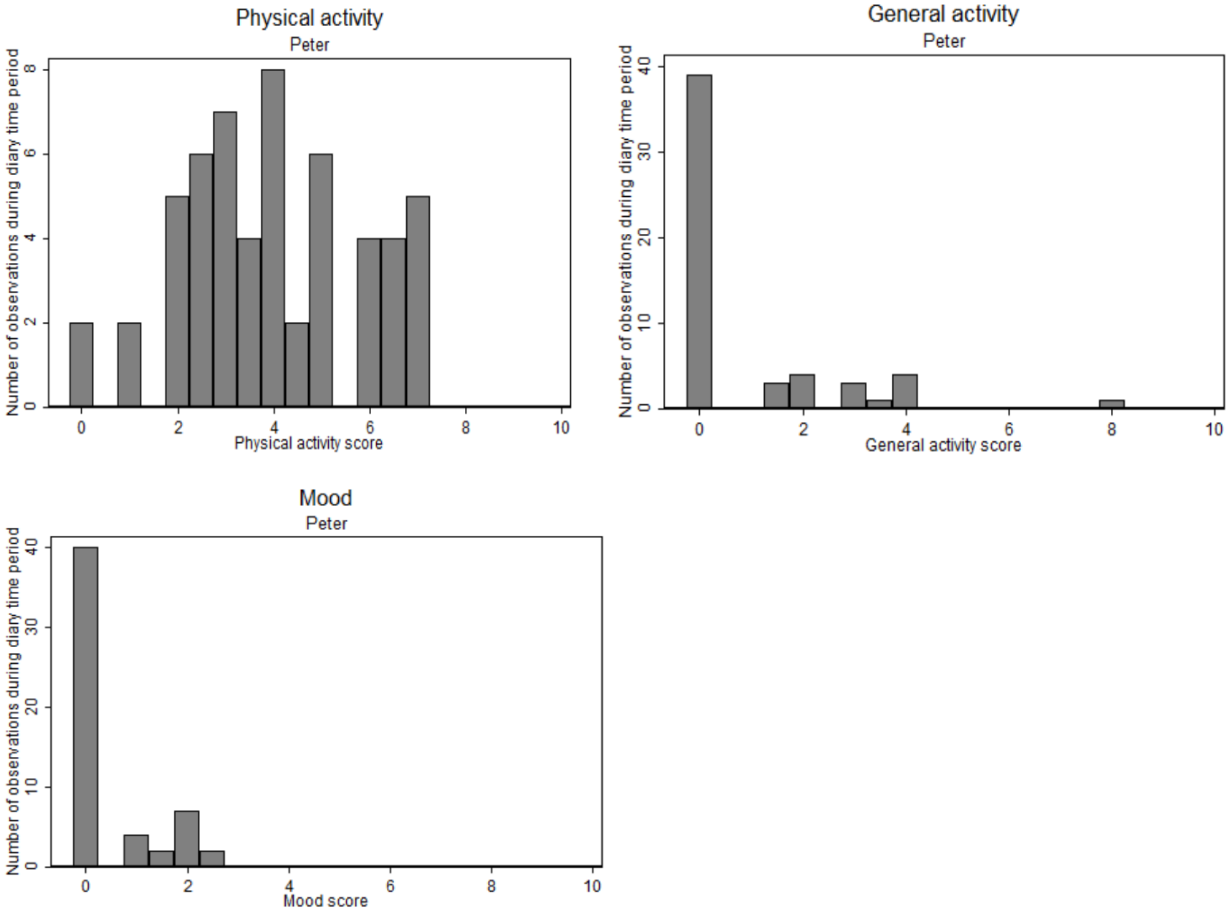
Peter reported good pain relief (Table 6.5.). Therefore, forty zero-values representing no pain were reported after pain medication, whilst 44 zero-values were registered after non-pharmacological

pain relief strategies. This corresponded well with the large amount of zero-values of pain intensity and frequency. The complete distribution of pain relief after medicine and non-pharmacological methods are illustrated in the histograms below.



Activity (physical and general) and mood

Peter completed four less observations of activity, compared to the other parameters. There are two zero-values among these 55 observations regarding physical activity that span from 0 to 7. In contrast, there are 39 zero-values and 40 zero-values respectively, among the 55 observations of general activity and mood. The fact that mood scores are closer to general rather than physical activity scores, suggests that coping with pain (e.g., playing or being with peers and family) plays an important role in pain experience. This will be further addressed in Chapter 7 and 8.



Symptoms and localisation of pain

Peter experienced pain several places (back, throat, chest and abdomen) during the study period. However, backpain was the main problem for Peter, which he reported in 32% of observations. Peter´s pain was more intense (pain score 6.5) and frequent (score 5.5) the last 2 days before his condition worsened and he temporary stopped completing the app.

Furthermore, Peter reported nausea throughout the study period. Nausea seemed to be quite aggravated some days, as he scored up to 7 on the 0-10 scale. In addition, mild constipation was reported in 32% of observations. Moreover, Peter reported moderate numbness in his fingers and feet during the first weeks of treatment. However, the most frequent reported symptom was muscle weakness in his arms in 93% of observations and his legs in 96% of them, respectively.

Pain management

Peter reported a limited use of pain medication. He took paracetamol 17 days during the study period whilst morphine was only reported in 2 observations, which were the days before his condition worsened. The non-pharmacological pain relief methods used by Peter were massage, heating pads and distraction. However, he only reported using these methods in a few observations.

6.4.2.4. Participant 4 (Thomas)

Thomas, a 15-year-old boy, participated for 11 days. During this time, Thomas completed four observations. This participant did not respond to chemotherapy, his condition deteriorated, and he sadly died a few weeks after the diagnosis.

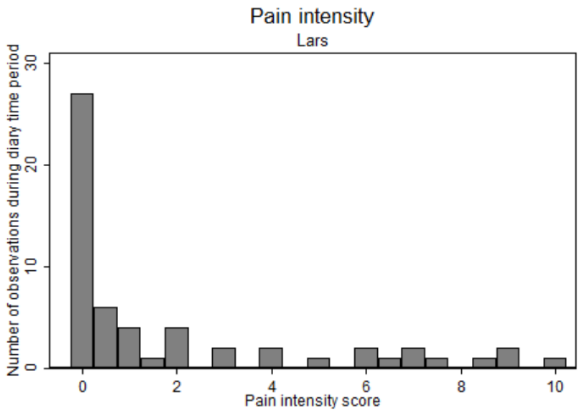
Pain intensity and frequency were zero in all observations. However, strength in both arms and legs was diminished scoring 5-7. In concordance, physical activity was reduced, scoring 5-5.5. General activity and mood were reported as normal (zero-value) except for the last observation, where general activity scored 4 and mood 1.5. There are no histograms for this participant due to the limited number of observations.

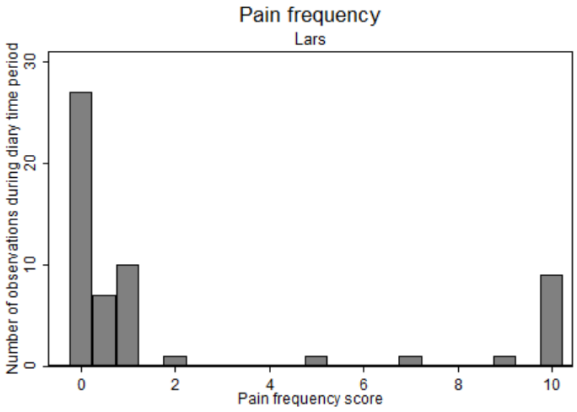
6.4.2.5. Participant 5 (Lars)

Lars was an 11-years old boy who participated in this study for 93 days and delivered 57 daily observations. He used the app perfectly well and was extremely interested in the technical details and its potential for improvement.

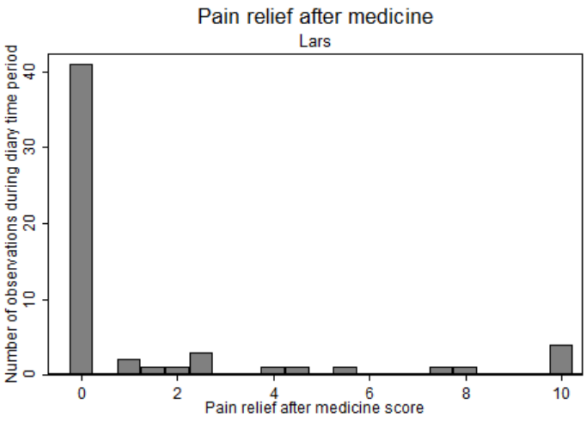
Pain intensity and frequency

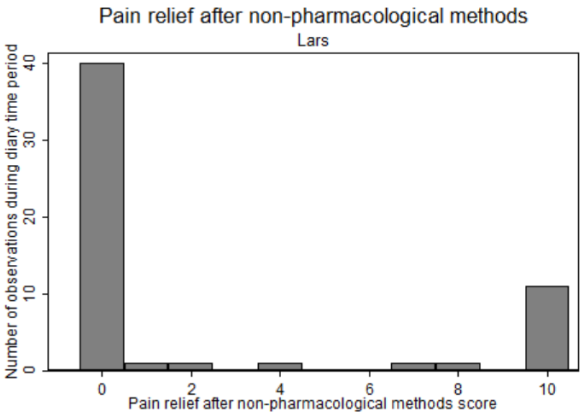
The histograms below indicate that Lars reported no pain in 33% observations. However, he also experienced days with high pain scores and the most troublesome problems were pain in the abdomen and anus. Lars reported good pain relief after pharmacological and non-pharmacological pain methods. Generally, Lars was in a good mood but intense pain had a strong impact on his emotions and activity level (both physical and general).



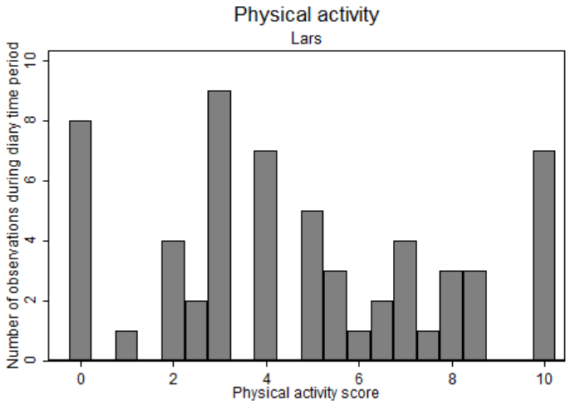


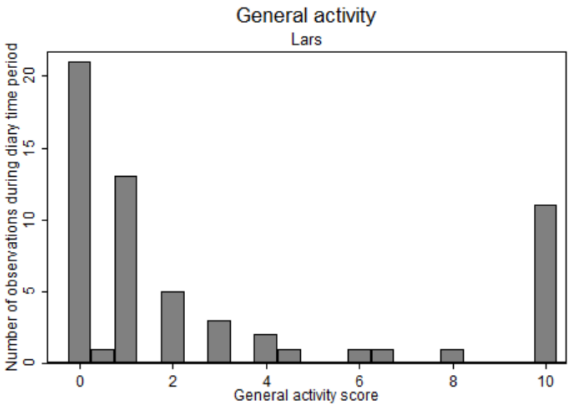
Pain relief

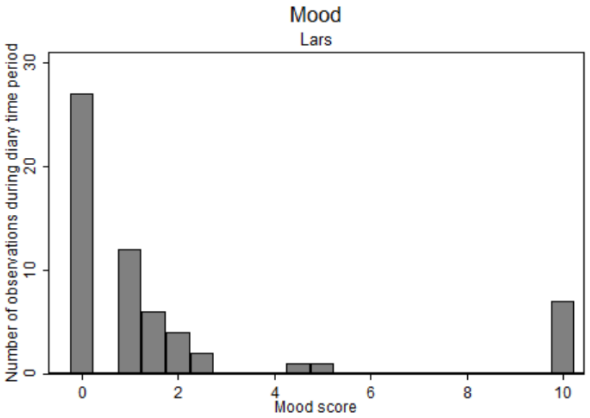




Activity (physical and general) and mood



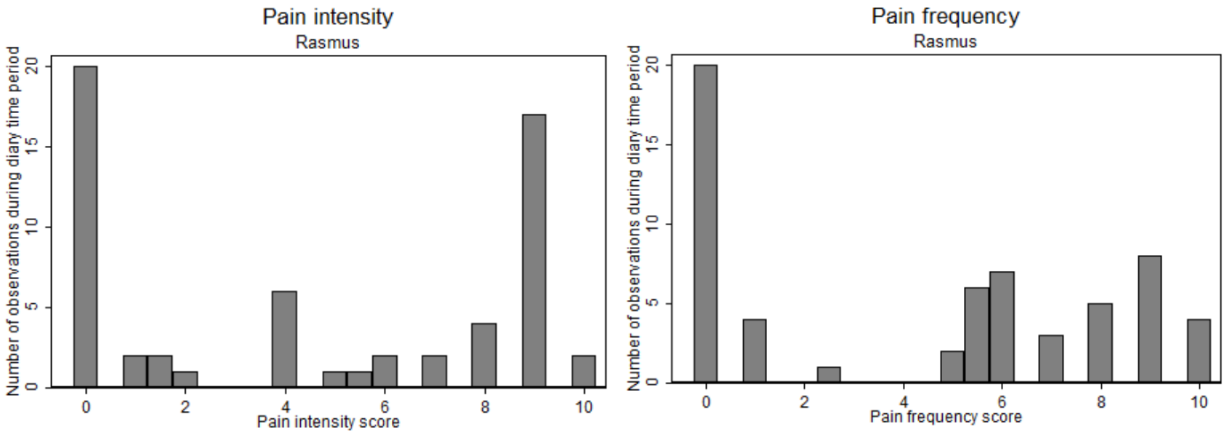




6.4.2.6. Participant 6 (Rasmus)

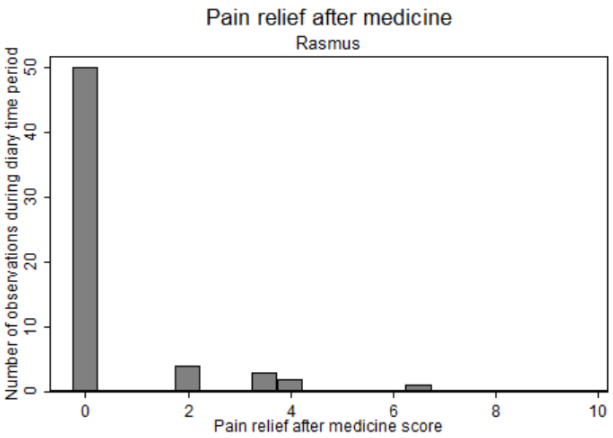
Rasmus was a 17 -years old boy, who participated in this study for 93 days and delivered 60 daily observations. He turned 18 years old during the study and after his birthday he provided his own written consent (parental written consent was obtained at the inclusion). Rasmus developed various adverse reactions to chemotherapy and he reported pain, especially abdominal pain towards the end of the study. His condition was serious for some time and he underwent surgery (appendectomy).

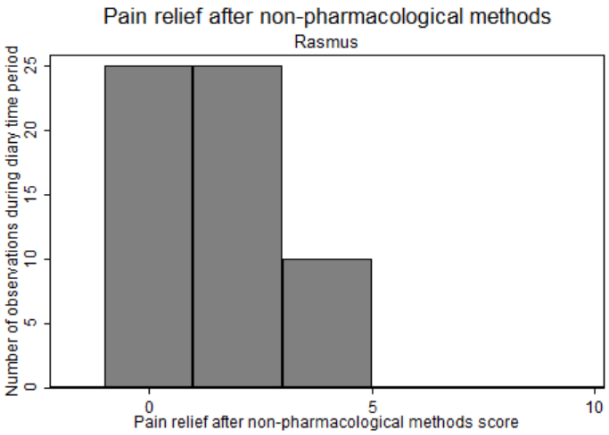
Pain intensity and frequency



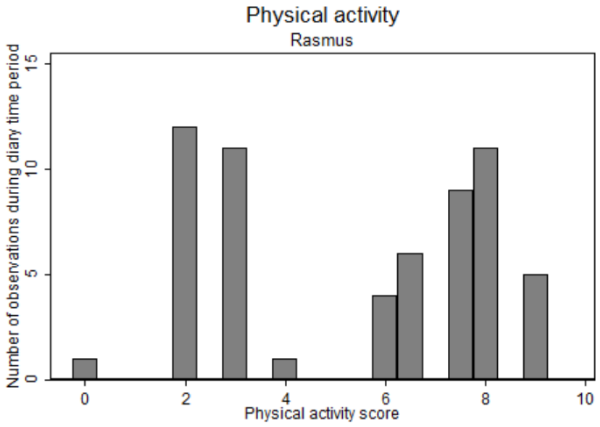
Pain relief

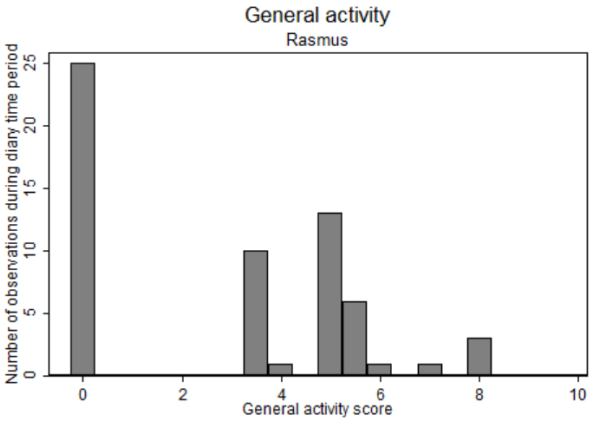
The histograms below indicate that Rasmus' pain relief strategies were effective, especially analgesic medication. Therefore, he reported zero values in 50 observations.

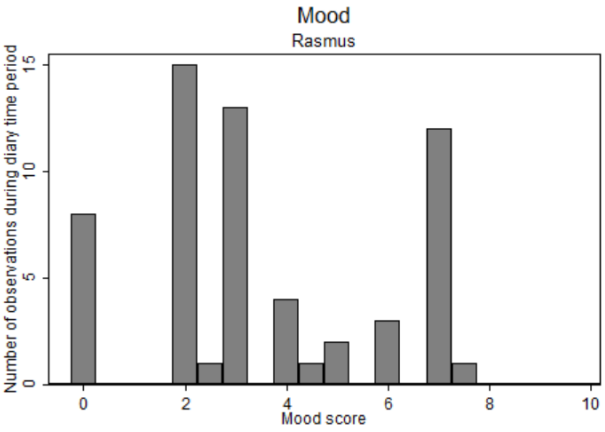




Activity (physical and general) and mood







Rasmus' activity and mood ratings demonstrated a wide variability, ranging 0-8. Parallel with pain levels, these parameters also reflect that his condition worsened during the last days of his participation in the study.

6.4.3. Overview of registrations

Overviews of sample registrations are illustrated in tables. Pain intensity and frequencies are presented in Table 6.2., which also includes zero-values pain ratings.

Table 6.2.

Pain intensity and frequency ratings

	Pain Intensity		**Pain Frequency**	
Measure	Mean (SD)	Zero values N and %	Mean (SD)	Zero values N and %
Laura	3.42 (2.89)	26 (31%)	3.74 (2.97)	26 (31%)
Victor	5.41 (2.28)	0 (0%)	4.59 (2.52)	0 (0%)
Peter	1.47 (2.37)	40 (67%)	1.11 (1.82)	40 (67%)
Thomas	0 (0)	4 (100%)	0 (0)	4 (100%)
Lars	1.96 (2.93)	27 (46%)	2.21 (3.75)	27 (46%)
Rasmus	4.54 (3.96)	20 (33%)	4.41 (3.77)	20 (33%)
All participants	3.25 (3.4)	117(46%)	3.17 (3.3.)	117(46%)

Note: SD= Standard Deviation, N= number of observations

Data in Table 6.2. demonstrate a wide variability in pain prevalence reported by children, which ranged from 0 to 100% of observations. Across all participants, pain was on average reported in 54% of observations (SD= 28.77) whilst 46% of pain intensity and frequency ratings were zero values which represented no pain.

Children experienced pain in different locations, which are illustrated in Table 6.3.

Table 6.3.

Localisation of pain

Localisation	Legs	Abdomen	Head	Throat	Back	Anus	Mouth	Chest	N
	Counts and % within total number of observations								
Laura	52 (62%)	12 (14%)	11 (13%)	7 (8%)	0	0	6 (7%)	0	83
Victor	44 (95%)	15 (32%)	0	0	0	9 (19%)	10 (21%)	0	46
Peter	0	2 (3%)	0	2 (3%)	19 (32%)	0	0	2 (3%)	59
Thomas	0	0	0	0	0	0	0	0	4
Lars	11 (19%)	10 (17%)	0	1 (2%)	2 (3%)	7 (12%)	0	4 (7%)	57
Rasmus	0	34 (56%)	39 (65%)	30 (50%)	10 (16%)	2 3%)	0	0	60

Note: N= total number of observations

Means across all participants indicate that pain was most frequently located in the legs (29%) and the abdomen (21%). This was followed by headaches (13%), pain in the throat (10%), back (8.6%), anus (5,6%), mouth (5%) and chest (1.6%).

Other symptoms closely related to pain experience ratings are illustrated in Table 6.4.

Table 6.4.

Symptoms

Symptoms	Constipation	Nausea	Mucositis	Numbness fingers	Numbness feet	Strength arms	Strength legs	N
	Counts and % within total number of observations							
Laura	13 (15%)	9 (10%)	13 (15%)	0	0	65 (78%)	83 (100%)	83
Victor	0	15 (32%)	12 (26%)	8 (17%)	46 (100%)	7 (8%)	46 (100%)	46
Peter	19 (22%)	36 (61%)	0	26 (44%)	26 (44%)	55 (93%)	57 (96%)	59
Thomas	1 (25%)	2 (50%)	0	0	0	3 (75%)	3 (75%)	4
Lars	9 (15%)	23 (27%)	0	36 (63%)	23 (40%)	40 (70%)	46 (80%)	57
Rasmus	38 (63%)	38 (63%)	25 (41%)	54 (90%)	54 (90%)	54 (90%)	54 (90%)	60

Note: N=Total number of observations

Means across all participants indicate that muscular weakness was the most frequent reported symptom, in the legs in 90% of observations and in the arms in 69%, respectively. Numbness in the feet was reported by 45% of children, while 35% reported numbness in the fingers. Nausea was reported in 41% of observations, constipation in 23% and mucositis in 13%.

Table 6.5. presents pain ratings after pharmacological and non-pharmacological pain relief strategies while Table 6.6. illustrates physical activity, general activity and mood.

Table 6.5.

Pain relief

Participant	Pain relief after medication		Pain relief after non-pharmacological methods	
	Mean	SD	Mean	SD
Laura	0.95	1.5	1.20	1.7
Victor	5.53	1.5	6.02	2.2
Peter	1.37	2.2	1.07	2.0
Thomas	0	0	0.25	0.3
Lars	1.45	3.0	2.36	4.1
Rasmus	0.55	1.4	1.67	1.7
Total	1.64	2.6	2.05	3.0

Note: SD= Standard Deviation

Table 6.6.

Physical activity, General activity and Mood

	Physical activity		General activity		Mood	
	Mean	SD	Mean	SD	Mean	SD
Laura	4.45	1.5	3.79	2.5	2.65	2.3
Victor	6.43	1.5	6.96	2.0	3.76	2.5
Peter	3.96	2.2	0.89	1.6	0.48	0.8
Thomas	3.88	0	1	2	0.38	0.75
Lars	4.75	3.0	2.92	3.8	1.89	3.1
Rasmus	5.40	1.4	2.9	2.7	3.53	3.3
Total	4.81	2.4	3.37	3.2	2.42	2.6

Note: SD= Standard Deviation

Table 6.7.

Pain management

	Pain medication				Non-pharmacological methods			
Pain Relief Methods	**Paracetamol**	**Morphine**	**Amitriptyline**	**Nortriptyline**	**Distraction**	**Massage**	**Heating pad**	**N**
	Counts and % within total number of observations							
Laura	49 (59%)	20 (24%)	0	0	4 (5%)	8 (10%)	0	83
Victor	44 (95%)	7 (15%)	45 (98%)	45 (98%)	46 (100%)	0	0	46
Peter	17 (28%)	2 (3%)	0	0	3 (5%)	12 (14%)	5 (8%)	59
Thomas	0	0	0	0	3 (75%)	4 (100%)	0	4
Lars	22 (38%)	15 (26%)	0	0	2 (45%)	1 (2%)	5 (9%)	57
Rasmus	35 (58%)	8 (13%)	0	0	14 (23%)	17 (28%)	2 (3%)	60

Note: N= Total number of observations

As illustrated in Table 6.7, five participants reported usage of pain medication. Paracetamol was the most frequently used analgesic, being reported in average in 46% (SD= 29.48, range 0-95%) of observations while morphine was used in 14% (SD= 9.67, range 0-26%) of observations. Thomas did not report any use of analgesic medication as he did not respond to therapy and his condition worsened rapidly before he died. When Thomas's ratings are excluded, the main use of analgesics is higher, showing that paracetamol was used in 55.8% (SD= 25.66, range 28-95%) and morphine in 16.2% (SD=8.28, range 3-26%) of the observations. Tricyclic antidepressants for neuropathic pain were only used by one participant, who also reported the most frequent and severe pain in the legs.

Findings using Mann- Whitney test

Participants in this study were either younger than 10 years old and their parents completed the app or older and could self-complete the app. The group of young children (group 1) is different compared to the group of older children (group 2) both in number of participants and the number of observations provided. Furthermore, in the younger group of children, the reports represent the parental perception of their child's pain. Looking at the average pain levels as well as the

histograms, in young children pain intensity and frequency seem higher than in older children. It seems reasonable to test this difference across age groups. Furthermore, the distributions cannot be characterised as normally distributed. Wilcoxon rank-sum test, also known as the Mann –Whitney two-sample statistic was used to test the hypothesis whether these two samples (that is, unmatched data) were drawn from the same underlying population i.e., the two samples are not different from each other. An alpha level of 0.05 was used for these tests. The results are illustrated in Table 6.8.

Table 6.8.

Results of pain ratings in children younger than 10 years compared to older children

	Group 1 (1-10 years) (N = 129)	Group 2 (10-17 years) (N = 180)	
Variables	**Mean (SD)**	**Mean (SD)**	**Z-Score**
Pain intensity	4.14 (2.85)	2.62 (3.42)	4.538***
Pain frequency	4.05 (2.85	2.54 (3.50)	4.675***
Pain relief after medication	2.59 (2.67)	1.09 (2.28)	5.610***
Pain relief after non-pharmacological methods	2.92 (3.00)	1.66 (2.82)	4.149***
Physical activity	5.16 (1.99)	4.71 (2.66)	1.885
General activity	4.92 (2.77)	2.25 (2.98)	7.712***
Mood	3.05 (2.44)	1.97 (2.62)	4.777***
Nausea	0.98 (2.33)	3.06 (3.37)	-6.527***

Note: N= number of observations; SD= Standard Deviation

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Since the p-value is < .001 on all variables except physical activity, it is possible to conclude that the two groups are in fact not drawn from the same population. Hence, the Mann-Whitney test demonstrates that there is a significant difference in reported pain between the two groups: children younger than 10 years, experience more pain intensity and frequency, less pain relief and poorer general activity and mood than older children. Young children also experience significantly less nausea than older children while the difference in physical activity is insignificant.

6.5. Summary

This quantitative study used a longitudinal approach to obtain knowledge about pain in children during the first three months of ALL treatment. Six participants completed pain diaries on a mobile

application, reporting daily data on pain characteristics and other symptoms related to pain, the use of pain relief methods as well as physical activity, general activity and mood. The discussion of findings from pain diaries is provided in Chapter 7.

7. Chapter 7 Discussion of Study 2

7.1. Overview of Chapter 7

This chapter provides a discussion of Study 2, "Pain variations and management in childhood acute lymphoblastic leukaemia*",* which was presented in Chapter 6. The first section discusses the pain diary findings. The last section addresses the strengths and limitations of this study.

7.2. Pain diary findings

This study sought to obtain knowledge about pain in children during the first three months of ALL treatment. Pain data was collected on a mobile application. Technically, participants could complete the app whenever they wanted, including multiple daily registrations. However, the app was only completed once daily and generally in the evenings when the participants could relax (e.g., with their smartphone).

7.2.1. Pain characteristics

Cause of pain

Participants did not make any notes regarding the disease course or treatment strategies (e.g., therapeutic procedures and chemotherapy administration). Therefore, the pain diaries do not provide any specific data about the cause of pain (disease- or treatment-related pain). However, it is most likely that the pain ratings in this study reflect the adverse effects of ALL treatment. This is consistent with previous research, which reports that pain in leukaemia is most frequently treatment-related (Van Cleve et al., 2004).

Pain Intensity

Mean pain intensity level reported in this study was 3.25 (SD=3.4, range 0-10). The highest mean pain score was 5.41 while the lowest was 0 on a 0-10 scale. These results are consistent with the findings of Van Cleve at al. (2004), who reported that most children regardless of age (4-17 years) experienced significant pain during the first year of leukaemia treatment. Therefore, for children aged four to seven, the highest and lowest mean scores, respectively, were two and 1.6 on a 0-4

scale, while for the children eight to seventeen, the highest and lowest mean scores, respectively, were 50.1 and 39.5 on a 0-100 scale (Van Cleve et al., 2004). However, the data collection method in Study 2 was different compared to previous leukaemia studies: the current study collected daily pain ratings during the first three months of ALL treatment while previous studies collected data at separate time points during the first year of treatment (Dupuis et al., 2016; Van Cleve et al., 2004). Real-time self-reports are expected to reproduce more precisely a child´s pain experiences compared to pain reports collected at various time points during participation time (Stinson et al., 2013).

Pain Localisation

Pain in the current study was mainly located in the legs, abdomen, head, throat and back. Within the total number of ratings, leg pain was reported in 29%, abdominal pain in 21%, head in 13%, throat in 10%, backpain in 8.6%, anus in 5.6%, mouth in 5% while chest pain was only reported in 1.6% of ratings. These findings are consistent with the literature, which found that the most common pain locations included legs (26.5%), abdomen (16.6%), head/neck (16.6%) and back (14.2%) (Van Cleve et al., 2004).

Other symptoms

Pain locations reported in this study are, according to the literature, frequently associated with medical procedures and chemotherapy drug effects (Toft et al., 2018). For example, pain, numbness and muscle weakness in the arms and especially the legs are often related to the administration of vincristine, which causes peripheral neuropathy (Moore & Groninger, 2013). In the current study, muscle weakness in the legs is reported on average in 90% of observations (SD= 9.67, range 75-100%), which means that this is the most frequently reported symptom**.** However, apart from peripheral neuropathy, there are also other conditions that cause muscle weakness (e.g. fever and reduced food intake) (Johnston et al., 2018; Ljungman et al., 2000) but these issues are not included in the topic of this study. An alternative explanation of the high prevalence of this symptom is that muscular weakness is easy to assess for children and their parents, while the assessment of other symptoms like nausea depends on the child´s ability to describe symptoms (Cheng et al., 2019). Therefore, children younger than five years old presented a lower nausea prevalence (mean 21%) compared to the older children (mean 50.25%) which is in line with the literature (Dupuis et al., 2016).

7.2.3. Pain management

Parents of children with cancer hold misconceptions about pain assessment and management, which impacts on their administration of analgesia (Fortier et al., 2012;Tutelman et al., 2018). However, parental understanding of pain and pain medication develops throughout a child´s disease and is related to the HCPs' capacity to educate and support families (Bettle et al., 2018). This in turn depends on HCPs' knowledge of pain as well as their perception of a child´s pain and anxiety and parental distress (Linder & Wawrzynski, 2018).

In the current study, paracetamol was the most frequently used analgesic being reported in average in 46% (SD= 29.48, range 0-95%) of ratings while morphine was used in 14% (SD= 9.67, range 0-26%) of ratings. Although the morphine usage across all ratings seems relatively low, all participants (except Thomas) reported having taken morphine at some point during the first 3 months of treatment. The findings in the current study suggest a higher use of morphine compared to the results of a study in India (Geeta et al., 2010). This study of 61 patients with ALL treated according to WHO guidelines demonstrated that of 39 children, who needed referral to pain and palliative care services, only six (15%) children required opioids. Fifty-four per cent of those children achieved good pain relief with non-opioid medication and adjuvants (e.g., paracetamol, antidepressants and gabapentin).

The results of the current study can be more closely compared to the study by Getz et al (2018), who found that 77.7% of children with leukaemia were exposed to opioids. This exposure was highest during the first treatment phases, reflecting higher patient acuity on diagnosis and greater treatment-related complications in those phases. This explanation was supported by the parallel increase in PICU utilisation. Furthermore, the opioid utilisation increased with age, but did not differ by gender, race or insurance status. Although the current study does not provide data on opioid exposure during severe complications and admissions to PICU, there is a high probability that during complications children received higher dosages of opioids to ensure sufficient analgesia.

The results regarding non-pharmacological pain relief methods in the current study show a relatively modest use of massage (mean=25%, SD=34.47, range 0-100%) and heating pad (mean= 3%, SD=3.81, range 0-9%). In contrast, all participants used distraction to reduce pain, (mean=42%, SD=35.49, range 5-100%). Notably, these results illustrate that distraction was understood differently: for some participants distraction signified everything that kept their mind

occupied, while others had different preferences depending on their age and temperament, such as playing computer games or drawing.

The literature suggests that at home, the most frequently used pain relief method in children aged one to six years old included familiar strategies from everyday life, like holding the child on the parent's lap, comforting the child and spending more time with them. In addition, Kankkunen et al (2003) found a significant relationship between parents' use of non-pharmacological pain relief strategies and a child's pain intensity and pain behaviour. Furthermore, some evidence reports that non-pharmacological pain relief methods were only used in a limited number of cases (26%) in children with cancer (Plummer et al., 2017) and hypnosis was the only method that resulted in statistically significant reductions in anxiety and pain (Nunns et al., 2018). Other studies indicate that nurses would like to increase the use of imagery, positive reinforcement, thermal regulation, massage positioning and distraction but various barriers limited their practice, such as workload/lack of time and the child's inability to cooperate (He et al., 2010; Sng et al., 2013). However, it was not the scope of this study to clarify whether the parents or HCPs initiated the use of non-pharmacological pain relief methods.

7.2.4. Activity and Mood

Research suggests that pain significantly impacts on children´s physical and emotional functioning as well as their quality of life (Eiser et al., 2017; Sung et al., 2011). Moreover, the influence of emotional distress is highest in the immediate postdiagnosis period (Sawyer et al., 2000).

In contrast, the results of the current study indicate that despite pain, which impacted on the level of physical activity (mean= 4.90, SD=2.4, range 3.88-6.43), participants reported a better level of general activity (mean= 3.37, SD= 3.2, range 0.89-6.96) and their mood was generally good (mean= 2.42, SD= 2.6, range 0.38-3.76). These findings suggest that the participants were in the process of learning to cope with pain and illness.

7.2.5. Pain reports in different ages

Results of this study find that parents of children younger than 10 reported that their children experienced more intense and frequent pain than older children. For example, as illustrated in Table 6.2., Victor aged 1.5 years reported the highest pain intensity (mean=5.41, SD=2.3, range 9-2) and frequency (mean 4.60, SD= 2.5, range 1-10). There is a theoretical possibility that Laura and

Victor's mothers completed the app both when the child's condition was stable and when it worsened (and pain was more intense). However, Victor's mother only completed the app 49% of the participation time. Most likely, some of the missing data occurred when Victor's condition worsened because when complications occur, childcare responsibilities increase and this may impact on completion rates (Molinaro & Fletcher, 2018). Thus, Victor's registrations in the app most probably represents days when his general condition was relative stable.

Furthermore, the children's young ages (Laura was five and Victor 1.5 years old) and their limited ability to explain their symptoms might have been an extra reason to increase parental anxiety. Therefore, there is a possibility that Victor's young age, crying and discomfort contributed to his mother's sense of helplessness and anxiety and had a strong impact on her experience of Victor's symptoms (Cheng et al., 2019). Evidence supports that parental anxiety influences their experience and interpretation of a child's pain (Sawyer et al., 2000). As with other conditions with chronic pain, parental anxiety is associated with pain-related disability in children and adolescents with cancer (Link & Fortier, 2016). Parental anxiety significantly predicts solicitous behaviours and influences a child's pain and quality of life (Langer et al., 2009; Peterson & Palermo, 2004). Nevertheless, there are differences between having a child with a benign chronic condition and the issue of a life-limiting diagnosis. The diagnosis of cancer leads to an existential shock for parents (Linder & Wawrzynski, 2018), who experience numerous challenges while trying to manage their child´s disease. The literature demonstrates that parents experience severe distress during the child's disease and PTSD symptoms are found in a considerable number of parents years after diagnosis (Norberg & Boman, 2008). Furthermore, high levels of parental anxiety during their child's disease are a significant predictor for post-traumatic stress symptoms (Best et al., 2001).

However, the consecutive sampling method led to the fact that all eligible children diagnosed with ALL at Aarhus University Hospital were approached during the study period and asked to participate in this study. It is possible that only families with good resources chose to participate in this study that required some effort (5-10 minutes every day to complete the app). Supposing that parents who participated in this study had good resources may contradict the suspicion that the mothers of Laura and Victor were more anxious, and their anxiety made them interpret their child's pain as very intense and frequent. Laura's mother completed the app 89% of the participation time, which was the highest among all participants. Of 83 ratings, Laura's mother reported 26 zero-values (no pain) which is equivalent to 31% of the ratings during the study period. Assessing her child as

pain free in 31% of ratings supports the idea that Laura's mother was not exaggerating or catastrophizing her child's pain.

7.3. Strengths and limitations

7.3.1. Strengths

A strength of this study is that the selection of parameters in the mobile application was driven by the researcher together with expert paediatric oncologist opinion and patient input. These experts and patients confirmed that children with ALL experienced highly troublesome symptoms, such as pain, and that it was crucial to measure and understand these symptoms. The reasons for this intention is that in children, agreement on symptom severity is more concordant for visible, physical symptoms, than for invisible symptoms like pain (Johnston et al., 2018; Leahy et al., 2018; Rodgers et al., 2019). The app used in this study is the first leukaemia app in the Nordic and Baltic countries and contributes to new knowledge in this area.

Another strength of Study 2 is the relatively high completion rates of the app, which was on average 57.8% (SD= 16.68, range 33-89%) of participation time. The variability in completion was due in large part to a low rate of completion by one participant, who sadly did not response to chemotherapy and died shortly after inclusion. Other studies reported higher response to pain reporting. For example, a study testing a symptom diary as a mobile application (Mobile Oncology Symptom Tracker) in 10 adolescents with cancer for three weeks reported a response rate over 90% (Baggott et al., 2012). Another study testing a smartphone app called Pain Squad in 40 adolescents over four weeks found a response rate of approximately 68.8 ±38% (Jibb et al., 2017). While these two studies presented a high response rate, they were completed during shorter periods of time, which may have inflated the reported completion rates. Although the response rate in the current study is lower than in existing literature, the participation time is longer than for other studies and this may have influenced the completion rates of the app. Furthermore, children in the current study completed the app during the most intense period of chemotherapy (shortly after ALL diagnosis) and this might have affected their response rates (Sawyer et al., 2000). Other studies testing pain apps included adolescents up to 2 years after diagnosis, which means that some of these participants had already developed pain coping strategies (Stinson et al., 2013). In addition, the mobile application in the current study had no audible alarm to remind the participants to complete the app and was not game-based and therefore less entertaining. Research regarding completion rates of

electronic pain diaries indicates that these rates are positively associated with shorter diaries, financial compensation and alarms (Morren et al., 2009).

Some of the missing data in the current study occurred during the weekends and holidays (e.g., Christmas) when the participants probably prioritised their time being together with their families and peers. Other missing data occurred when a child's condition worsened, and the participants did not have the energy to complete the app. Thus, one participant (Peter) had a break due to admission to PICU. He wished to complete the app again when his condition became stable. Peter felt that it was important to participate in a project that could improve knowledge about ALL. Furthermore, the large number of zero-values that represent no pain suggests that the participants completed the app when the condition was relative stable. However, the fact that the participants most probably completed the app when their (or their children's) condition was stable might have biased the results. Thus, the level of pain intensity and frequency as well as the use of pain medication could have been higher if the participants completed the app while the condition was unstable, for example during admission to PICU (Getz et al., 2018).

The participation time in this study (three months of ALL treatment) is a strength and a contribution to new knowledge. Leukaemia treatment is known to be exhausting for both children and parents (Van Cleve et al., 2004) and extended projects based on self-reporting may be challenging for these families. Furthermore, engaging children and their parents in an electronic symptom self-reporting process is still a new method. In this context, three months is a relatively long surveillance time compared to other studies of electronic self-reports in paediatric oncology (Wesley & Fizur, 2015).

7.3.2. Limitations

Study 2 has several limitations. One limitation is that this study does not provide information about the setting where the participants reported pain (at home or in-hospital) due to the simple design of the app that did not include questions about the setting in which the current pain is experienced. Previous research has found that children's cancer pain was not optimally managed in the home setting where parents are largely responsible for children's pain management (Fortier et al., 2014). It was suggested that this might be because the parents did not accurately assess their child's pain or that the parents did not provide analgesia even when they detected child's pain due to misconceptions about pain medication. For example, parents believed that it was best to avoid pain medication because they were concerned about addiction and the side effects of analgesics (Fortier

et al., 2012). In the present study, across all participants, pain was in average reported in 54% of the ratings and the pain intensity was 3.25 ± 3.4 on a 0-10 scale before administration of pain relief strategies and 1.64 ± 2.6 after medication. The use of paracetamol was reported in average in 46% of the ratings while morphine was used in 14% of ratings. This means that the children received paracetamol in 85% and respectively morphine in 25% of the occasions when they (or their parents) reported pain. Furthermore, all participants except one boy who died shortly after inclusion in this study, reported taking morphine during the first three months of treatment. In addition, all children used non-pharmacological pain relief strategies, among which distraction was the most frequently reported (section 7.2.3.). Moreover, children older than 10 years self-reported pain and the use of analgesics and had assumingly the opportunity to influence the level of pain relief they received. Although this study did not identify whether the children experienced pain in-hospital or at home due to the simplicity of the app, the results demonstrated that the children received pharmacological and non-pharmacological pain relief in the majority of occasions when they (or their parents) reported pain and that the pain management strategies tended to reduce this pain. However, previous studies have showed that children with cancer experienced significant pain despite parents' use of pain management strategies (Tutelman et al., 2018). The present study is unable to distinguish differences in pain reports at home versus in hospital and which factors might improve a child's pain management at home. It is therefore important that future research records the setting in which children experience pain and includes further information around the context of this pain.

A possible limitation of this quantitative study is the lack of information about the cause of the pain reported in the app. The participants made no notes about any painful procedures. In addition, the registration of chemotherapy administration was optional and was completed infrequently. Therefore, this study did not capture the variations of pain depending on the timing of chemotherapy administration, which is associated with aggravation of pain (Gedaly-Duff et al., 2006). However, the results of pain diaries showed that pain was most frequently located in the legs (in average in 29% of observations) which is often associated with peripheral neuropathy, an adverse reaction to chemotherapy (Moore & Groninger, 2013). In addition, the symptoms associated with pain (e.g., nausea) are often caused by chemotherapy. Therefore, most likely, the pain reported in this quantitative study was treatment related. This finding supports previous studies that document treatment as the major source of pain in children with leukaemia (Hockenberry et al., 2017; Van Cleve et al., 2004).

Another possible limitation is that the participants were asked to complete the app once daily. Although the participants could complete the app whenever they wanted, including making multiple registrations each day, the app was typically completed by participants once a day in the evenings. The reason for this time of completion might be that the children and their families were busy during daytime with multiple diagnostic and therapeutic procedures. For example, blood tests and administration of chemotherapy require repeated painful venous punctures before the children would have implanted a central venous catheter, which significantly improves the daily painful routines (Tremolada et al., 2005). Furthermore, the wording of the questions in the app ("How is your pain today?") was more likely to get registration of longer lasting pain rather than brief periods of pain. Therefore, the researcher assumed that the pain ratings most likely reflected a child's average pain occurred over the duration of one day (24 hours) rather than the pain at the time of the specific interventions the child experienced during the day (e.g., venous puncture). This assumption might raise questions about potential recall bias, which have been associated with overestimations of pain (Morley, 2016). However, across all participants, a rating of no pain (intensity and frequency) was reported on average in 46% of ratings, which contradicts a tendency to overestimate pain. Moreover, asking the participants to complete the app at the time whenever they experience any pain would be a burden for participants who are particularly fatigued and would interfere with the activities of daily living. Also, when participants experience severe pain, although this might be a trigger to think about the app, it is questionable as to whether they would want to complete the app at that moment because of the pain and related symptoms being experienced in the moment. In addition, the interpretation of multiple daily pain episodes would require more data (several questions in the app) to illustrate the emotional climate when pain is occurring and how the children managed that pain (Stinson et al., 2013). Completing several questions would require longer time to register in the app every day, which would negatively influence the completion rate (Morren et al., 2009). Ultimately, the researcher had to assume that the pain scores reflected a child's average pain occurred over the duration of one day because the participants were not asked specifically to give an average of their pain, or the pain they felt right then. Future research with this app should clarify this point by specifically instructing people to rate their pain for the whole day as well as rate their pain in the moment (e.g., painful interventions).

The app utilises brief measures of pain. It is possible that more comprehensive measures would have captured better the characteristics of children and parents (e.g., anxiety). However, the use of a

visual pain scale is reliable and well documented in paediatric pain assessment (McGrath et al., 1996).

Another limitation is the small number of participants in Study 2. The researcher expected most of the children diagnosed with ALL during the participation time would be eligible and could be approached and informed about this study. However, only 10 children were approached during 1½ years and of these 10 children only seven accepted to participate in this study. Of these seven participants, two did not response to therapy and died shortly after inclusion. Furthermore, the age of the children included in this study ranged widely between 1.5 to 17 years (mean =10.9, SD= 4.4). These problems reflect the challenges met by clinical research and especially research that investigates rare and potentially fatal conditions in specific populations. Paediatric oncology populations are small and non-homogeneous for many reasons, such as different courses of treatment and a child's developmental stage. Furthermore, recruitment may be challenging (Hein et al., 2015), settings and outcomes may differ and comparisons between treatments may be difficult (Mercadante & Giarratano, 2014; Twycross, Forgeron, et al., 2015).

The recruitment of participants met several challenges despite building up a specialist network, which facilitated contact with the Danish paediatric departments. Therefore, many resources and trips to each study site were required to arrange workshops and meetings at the four paediatric wards in four different cities. In addition, it was not possible to obtain any funding to support this research and this has, most likely, influenced the number of local resources spent on approaching potential participants.

Moreover, the recruitment of participants in Study 2 relied on HCPs acting as gatekeepers to ensure potential participants were not approached at times when recruitment may have incurred additional distress (Linder & Wawrzynski, 2018). This strategy was a safety mechanism designed to reduce distress and overcome a potential ethical barrier (Section 6.2.1). However, it is not possible to say definitively whether HCPs fully understood potential participants' needs in these circumstances or the impact of research on participants. Indeed, some HCPs may have prevented potential participants from experiencing the potential benefits of involvement in this research despite ethical, professional and organisational approval (Leahy et al., 2018). Additionally, this may have influenced the number of participants included in this study.

Inclusion of participants stopped after participants 5 and 6 (pseudonyms Lars and Rasmus, as illustrated in table 6.2). The number of participants included at this point seemed sufficient to collect useful information for practice and further research, as well as completing the PD study in the time allocated. Although a study based on six participants can be considered a small sized study (Hackshaw, 2008), pain diary completion rates ensured a large number of ratings from participants with a relevant age-span for ALL (Toft et al., 2018). Therefore, this study with few participants sought to address the research question in a relatively short time and was conducted without external funding.

7.4. Summary

This chapter provides a discussion of Study 2. Pain diary findings are discussed in the light of existing research. Finally, strengths and limitations of this study are presented together with its contribution to new knowledge.

However, the quantitative approach adopted in Study 2 may overlook important aspects of a subjective experience that involves both child, parents and the HCPs taking care of these families. Therefore, the quantitative results of Study 2 will be integrated with the qualitative findings from Study 1 through interpretation in the next chapter, the “mixed-methods” discussion.

8. Chapter 8 Mixed methods Discussion

8.1. Overview of Chapter 8

This chapter will draw together the results from both qualitative and quantitative parts of this mixed methods study, to provide a comprehensive picture of the issues regarding pain experience and management in children with ALL. The conclusions will be discussed in the light of existing research, with a particular focus placed on highlighting the new contributions of this thesis. This will be followed by examining the strengths and limitations of this programme of research, contribution to new knowledge and implications for clinical practice. Finally, recommendations and future research, reflective perspectives and a summary of this thesis will be presented.

8.2. Mixed methods integration

Using a mixed-methods approach to integrate the results from Study 1 and 2, the researcher sought to understand the experience of pain and its management during ALL from multiple perspectives, including those of children, parents and clinicians. The research in this thesis presents a new combination of exploring a child´s pain experience qualitatively in interviews and quantitatively in measurements on a mobile application.

In Study 1, findings from interviews conducted with mothers and fathers as well as nurses and doctors from the paediatric oncology department and PICU contribute to existing knowledge, regarding the complexity of pain assessment and management in ALL.

In Study 2, the child´s voice is captured in daily pain ratings reported on a mobile application by children older than 10 years and parents of children younger than 10 years. These pain ratings demonstrated the individual variations in pain, symptoms related to pain, activity and mood. Real-time data collection during three months of ALL treatment is a new approach that adds knowledge to this area.

Data from Study 1 and 2 were analysed simultaneously but separately and the results were integrated during interpretation (Zhang & Creswell, 2013). During the course of leukaemia, children undergo many therapeutic procedures and their parents hold many additional caring responsibilities making their availability limited (Molinaro & Fletcher, 2018). Therefore, to avoid extensive parental burdens associated with participation in two pain research studies, different

samples of participants were used to collect the quantitative and qualitative data sets. Triangulation between the researcher's view, parent/HCPs perspectives and a child's report was used to secure the in-depth understanding of the phenomenon in question (Denzin, 2012).

An overview of the qualitative and quantitative findings is presented in Table 8.1.

Table 8.1.

Overview qualitative and quantitative findings

Qualitative findings **Themes**	**Subthemes**	**Data segment**	**Quantitative findings** **Daily reports on pain (0-10 scales)**	**Interpretation**
Complexity of pain assessment This theme outlined the challenges of parents, nurses and doctors when they assessed children's pain and what influenced their assessment.	**Signs of pain** This subtheme highlighted the manifestation and recognition of pain. Participants described the causes of pain, such as painful procedures and adverse reactions to therapy. They also described very intense and long-lasting	*"I think a child is in pain when he or she changes behaviour but also when I know that a child undergoes a treatment which causes pain". N1*	Children older than 10 years and parents of children younger than 10 years completed pain diaries on a mobile application. Pain was reported in average in 54% of registrations and had various intensities (mean 3.25) and frequencies (mean 3.17). There were differences in pain reports between individuals (the highest mean pain intensity was 5.41 and the lowest was 0). The participants	The qualitative data showed that pain in childhood ALL was mainly caused by invasive procedures and adverse effects of chemotherapy (e.g., mucositis and peripheral neuropathy). The children experienced very intense pain that was long-lasting. Contrastingly, the quantitative data demonstrated that there were differences in the pain intensity reported across the children included in this study, however, most children reported long-lasting pain. The symptoms associated with pain (e.g., constipation) were variable. Although the cause of pain was not captured in the app due to the simple design of it, the reports of pain and other symptoms associated with pain are concordant with the interview findings. These findings support previous work that has shown pain is a common symptom experienced by children with ALL (Van Cleve et al., 2004). Moreover, these results have confirmed that children experienced several other

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	pain and other symptoms.		registered different levels of other symptoms closely related to pain (constipation, nausea, mucositis and muscle weakness).	bothersome symptoms, which are variable during the course of ALL (Hockenberry et al., 2017). Furthermore, in interviews, HCPs and parents emphasised that every child experienced his/her own pain trajectory during ALL. The results of pain diaries supported the qualitative data documenting that the pain characteristics and associated symptoms varied among patients. These findings are in line with the International Association of Study of Pain (IASP) definition of pain, which acknowledges that pain is always a personal experience (IASP, 2020).
	Frequent mentions of pain in the abdomen, legs, mouth/throat, head and bottom (anus).	"*She suffered from several infections and severe inflammation of the intestines." P4*	Most frequently, children reported pain located in the legs (29%), abdomen (21%), head (13%), throat (10%), back (8.6%), anus (5.6%), mouth (5%) and chest (1.6%).	Analysis of interviews found that the children experienced severe pain in different parts of the body (legs, abdomen, head, throat/mouth, back and anus). The quantitative data showed that the locations of pain reported by children or their parents were similar to those described in the interviews. However, there was a difference between the two data collection methods: the interviews highlighted the abdominal pain and the potential complications associated with it. The findings regarding the locations of pain are

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				consistent with the results of Van Cleve et al (2004), who interviewed parents and children during the first year of ALL treatment. Moreover, these locations of pain supported the assumption that both qualitative and quantitative data primarily reflected the more long-lasting pain associated with adverse effects of chemotherapy.
	Pain had a strong impact on a child´s behaviour.	*"Small children cry, or they don't want to eat. Some of them are restless and some of them lay down and do not move. "D3*	The pain diaries demonstrated that pain impacted different aspects in a child´s life: physical activity (mean 4.81, general activity (mean 3.37) and mood (mean 2.42).	The qualitative data showed that pain had a strong impact on a child's behaviour. Pain affected a child's mobility, eating habits, social activities and mood. The quantitative data demonstrated that pain impacted both physical (e.g., play, run) and general activity (e.g., being with friends) as well as mood. The interpretation was that both qualitative and quantitative results demonstrated that pain significantly impacted children's day-to-day life. These findings are consistent with the results of Earle et al (2007) that noted in childhood ALL the detrimental effects of pain on physical activities and social interactions of children. Pain impacts a child's social functioning in various paediatric chronic pain conditions. In a synthesis of qualitative studies regarding

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				adolescents with chronic pain, Jordan et al (2017) identified negative outcomes associated with social isolation such as poor emotional functioning and a lack of availability of peer support and understanding. Furthermore, Myers et al (2014) showed that depressive symptoms were a significant problem from the end of the first month of ALL therapy to 12 months after diagnosis.
	Parental interpretation was the main source of information for HCPs when small children could not describe their symptoms.	*"It is so difficult to understand pain that is why we involve the parents especially for small children. "D1*	In this study, children older than 10 years provided self-reports while pain in younger children was reported by their mothers. According to maternal reports, children younger than 10 years had higher pain intensity than older children but experienced similar reductions in	The findings from interviews emphasised the challenges HCPs encountered when the stage of children's cognitive development affected the HCPs' understanding and interpretation of pain. In the quantitative study, mothers completed the pain reports in children younger than 10 years while older children could provide self-reports. These findings are in line with previous studies that highlighted parents as the main source of information in children unable to report the pain due to young age or illness (Cheng et al., 2018). Although findings from interviews supported the recommendations of von Bayer (2006) that children as young as five years of age were able

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			physical activity. These results suggested that parental reports were effective but possibly not identical to children's self-reports.	to report pain, in the quantitative study the parents acted as proxy for children younger than 10 years to compensate for children's possible limitations (lack of reading abilities and understanding of pain medication). Nevertheless, findings from both studies recognise the role of collecting self-reports from children whenever possible.
	Understanding a child's pain expression required that HCPs had a good knowledge of the child´s psychosocial background.	"*What is their normal behaviour and when do they behave as they do because of their disease or their medicine? Or is it because they cannot cope with the situation?" N1*	Pain diaries showed a substantial reduction in children's physical activity due to pain. The impact of pain on general activity and mood was moderate. Although physical problems were common, there were differences in general activity and mood reports. For example, one participant reported a high	Analysis of interviews indicated that HCPs needed a good knowledge of a child´s psychosocial background to understand the child's expression of pain. Results from pain diaries found that pain had a substantial impact on children's physical activity (e.g., play, run) but only a moderate impact on general activity (e.g., be with friends) and mood. Furthermore, the results from pain diaries showed differences in participants' reports of general activity and mood. The social communication of pain model was considered in relation to these findings as it addressed the social context where a child's pain was expressed, assessed and responded to (Craig, 2009). However, biological factors as age and

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			level of general activity (mean 0.89) and good mood (mean 0.48) while another participant reported a lower level of general activity (mean 2.9) and mood (mean 3.53).	illness needed to be included in the assessment of pain as recommended by Turner-Cobb (2014). For example, the child's age, the disease and certain types of medication (e.g., corticosteroids) could directly impact the child's behaviour and ability to cope with pain. These findings highlight the importance of looking at both psychosocial and biological factors in the assessment of pain.
	HCPs emphasised that accurate symptom assessment was vital as this had implications for both diagnosis and pain management decisions.	*"I think we are good enough at asking about pain and maybe start pain treatment, but I do not think we are good enough at documenting and evaluating the effect of pain management. Although pain scores*	Data from pain diaries indicated that children older than 10 years and parents of young children were able to provide pain ratings and estimations of pain relief.	In interviews, HCPs described the importance of assessing and documenting a child's pain and the effect of pain relief methods. HCPs considered the child's self-reports and/or parental perceptions of that pain as essential in pain assessment. Results from pain diaries demonstrated that children older than 10 years and parents of children younger than 10 years were able to report daily data on pain and other symptoms, the use and effect of pain relief strategies and levels of activity and mood. However, according to interviews, HCPs documented children's pain infrequently. These results fit well with the findings of Twycross et al

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		are easy tools they are not used sufficiently. Sometimes it's just the nurses' evaluation." N5		(2015), who found infrequent documentation of paediatric pain assessment and management in the clinical setting. Furthermore, this data show in combination, that HCPs find it hard to document pain ratings, whereas children or their parents find it relatively easy and this is something that perhaps patients could be called upon to do more. Thus, the findings in this research study demonstrated the need to incorporate the child's and parents' voice in pain assessments whenever possible, which supports the recommendations of Turk & Melzack (2011).
Anxiety and fear for the unknown This theme focused on children's and parents' anxiety as well as	**Pain as a mask for psychological distress** This subtheme outlined the close relation between psychological	*"Sometimes they lie in bed with their head under the pillow and they don't want to talk. They are sad and depressed. It is easier to say "I am in pain" than express*	Findings from pain diaries indicated that children younger than 10 years, as reported by their mothers, experienced significantly more intense and frequent pain than those older than 10 years. Moreover, mothers reported that their	The qualitative data showed that it was sometimes difficult for HCPs to understand a child's pain. Different expressions of pain due to the child's age, illness or emotional distress complicated the interpretation. Moreover, in interviews HCPs described that older children expressed more pain while in pain diaries the mothers of children younger than 10 years reported the opposite: their children experienced significantly more pain than the older children.

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clinicians' worries regarding pain management.	distress and pain. HCPs described that older children expressed more pain than younger children. Withdrawal and introversion were often described as a sign of pain in those children and adolescents. When older children expressed	*feelings. We have had some unpleasant cases where we treated pain due to psychological distress with painkillers. Difficult to interpret." D1*	children experienced less pain relief after both pharmacological and non-pharmacological pain relief methods.	These findings can relate to the social communication of pain model that focuses on a child's expression of pain in a social context where the child interacts with parents and HCPs (Craig, 2009). Collins et al (2000) and Zernikow et al (2005) reported a good agreement between a child's and parents' report in childhood cancer. However, Zhukovsky et al (2015) reported significant differences between reports of adolescents and their parents. Although the parents might overestimate their young children's pain, parents spend more time with young children and have more opportunities to observe their child's condition. The findings in this research support previous results showing that older children and adolescents might experience more emotional distress, which could be perceived as pain (Woodgate & Degner, 2003). Furthermore, the findings are consistent with the conclusions of Leahy et al (2018), who argued that emotional distress was more difficult to assess than physical signs of pain.

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	higher than anticipated levels of pain, HCPs perceived this as a considerable challenge.			
	Children (and parents) admitted to the PICU experienced high level of anxiety and distress.	*"Children with leukaemia admitted to the PICU often have a severe physical pain problem but sometimes other factors have made the pain worse… they have a severe disorder associated with a major fear of*	Children completed the app on average 57.8% (SD= 16.68, range 33-89%) of participation time. The relatively large variability in completion was due to a low rate of completion by one participant, who sadly did not respond to chemotherapy and died shortly after inclusion.	Analysis of interviews showed that children and their parents experienced a higher level of anxiety and distress during an admission to PICU. Quantitative data showed that there were periods of interruption to diary completion. However, the pain diaries did not provide information about the cause or the setting (in hospital or at home) where these interruptions occurred. Although the reason of not responding could not be identified, some missing data might have occurred when children´s conditions worsened (e.g., admission to PICU), which was understandable as children might have been extremely tired or even sedated and mechanically ventilated. There could be times when

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		death… We have children who are very anxious and children who have difficulties in understanding they are very ill. We have some parents and relatives who are generally very tense, they are under the intense ongoing pressure of having a child who is so ill." N3		completing the app was not appropriate, either because the questions in the app were not relevant for the child's condition or due to the high level of anxiety and distress the family was experiencing. These findings support the results of Hockenberry et al (2017), who found that the trajectory of paediatric malignancies often involved unexpected complications as well as plateaus of relative stability. In addition, the child-parent experience of admission to PICU can relate to the work of Colville (2012) who described how distressful the experience was for the whole family.
	Clinicians´ concerns and uncertainty	*"It feels difficult for the whole team. When it is a case like this, it feels*	Results from pain diaries demonstrated that children often experienced good pain relief: mean pain	Findings from interviews showed that HCPs were concerned not being able to effectively manage pain especially when working with patients with complex care needs. In contrast, data from pain diaries suggested that

Qualitative findings			**Quantitative findings**	**Interpretation**
Themes	**Subthemes**	**Data segment**	**Daily reports on pain (0-10 scales)**	
	This subtheme addressed HCPs concerns about best practice for managing pain in children with ALL. HCPs worried about "not doing enough" to alleviate pain.	*distressing that you cannot ease the pain. When they are in so much pain, and you cannot help them, you cannot do it well enough…this feeling is difficult." N4*	score after pain medication 1.64 and 2.05 after non-pharmacological pain relief methods.	most children with ALL achieved good pain relief on most occasions. One explanation of this discrepancy might be a recall-bias in interviews. According to Morley (2016), participants' memories largely reflect the worst intensity of pain they remembered. Jibb et al (2017) argued that electronic pain diaries minimised recall bias. Another explanation might be that it was only natural that HCPs worried at times whether they have done enough for their patients with ALL where a number of children did not survive. The doctors and nurses highlighted their responsibility for numerous treatment decisions, which caused substantial moral load. Given that HCPs (especially the doctors) routinely did not document pain ratings means that they could only rely on their perceptions, which could be coloured by other emotional factors (like moral load). The findings in the present study agree with the results of Linder & Wawrzynski (2018), who described HCPs' challenges associated with symptom perception and distress

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				when HCPs and families had a divergent perception of a child's pain.
	Opioids and their use in children were challenging issues for HCPs	*"We must find the balance because the more we give morphine the more the child gets constipation and cramps. I think it's one of the most difficult things in my job because we do not know enough about it." D4*	Nausea was reported on average in 41% and constipation in 23% of the ratings. During pain management with morphine, nausea was reported on average in 55% of observations, (range 5-100%) while constipation was reported in 22% (range 0-100%) of observations.	Interview findings showed that HCPs were concerned about the adverse effects of treatments, the etiology of pain and the most appropriate pain management strategy. The results from pain diaries confirmed that children often experienced pain and other symptoms related to pain. Pain was reported on average in 54% of observations and had various intensities (mean 3.25) that diminished after pain medication (mean1.64). Morphine was used on average in 14% of observations and it was always reported together with paracetamol and non-pharmacological pain relief (e.g., distraction) so it was not possible to evaluate its separate effect on pain. During pain management with morphine, nausea was frequently reported but data from pain diaries showed a large variation: one participant was excluded from this calculation because he reported no use of morphine but he reported nausea and constipation before he sadly died shortly after inclusion. Other participants reported nausea in

Qualitative findings **Themes**	**Subthemes**	**Data segment**	**Quantitative findings** **Daily reports on pain (0-10 scales)**	**Interpretation**
				100% of observations during morphine treatment. Constipation was a less frequent symptom and was only reported in 100% of observations while taking morphine by one participant, who needed abdominal surgery after a few days with pain, nausea and constipation. Data from pain diaries demonstrated that nausea and sometimes constipation were associated with pain that might require opioids. However, quantitative data could not identify the cause of these symptoms, such as chemotherapy, opioids or the disease itself. These findings support previous works that highlighted HCPs concerns with opioids (Friedrichsdorf, 2017) and were interpreted as a continuous need of pain education among HCPs.
	Parental concerns regarding strong medication	*"They think of their own fear of addiction and believe this would happen to their child. We must explain to them that*	The pain diaries reported that paracetamol was the most frequently used analgesic medication being reported in 46% of observations, while	The interviews identified parental concerns associated with the use of opioids for pain control including fear of side effects and addiction. However, most parents had changed these attitudes over time as parents learned more about their child´s disease and gained confidence in using pain medication to relieve their child's pain. The results of pain

Qualitative findings			**Quantitative findings**	**Interpretation**
Themes	**Subthemes**	**Data segment**	**Daily reports on pain (0-10 scales)**	
	This subtheme emphasised parental concerns and attitudes toward pain medication reflected their beliefs. HCPs described that parents believed opioids were related to addiction and social stigma.	*sick children do not get addicted in the way they fear, and they will be morphine free when they get better." N1*	morphine was used in 14% of observations. However, all children (except Thomas) reported using morphine at some point during the study period.	diaries showed that the children received pain medication on most occasions when they reported pain. In this study, the findings regarding parental misconceptions about the use of pain medications were not associated with parents not providing analgesics to their child. This is in contrast to prior work in the area of parent pain management, which has found that parental negative attitudes were associated with the administration of fewer analgesics (Fortier et al., 2012; Rony et al., 2010).
	Parents thought pain medication influenced the child's condition and	*"Pain medication is good, but you must take care, it is like a bad circle … My wife and I think that*	The participants reported they used both pharmacological and non-pharmacological pain relief strategies to	Interview findings highlighted a strong parental desire to be involved in their child's treatment including the need to control pain medication and its adverse effects. Although parents preferred the use of fewer analgesics, they did not fail to respond when their child was in pain and they

Qualitative findings			**Quantitative findings**	**Interpretation**
Themes	**Subthemes**	**Data segment**	**Daily reports on pain (0-10 scales)**	
	sometimes they preferred their child to tolerate pain. Parents preferred non-pharmacological methods to relieve pain.	*medicine is good but used when it is only really needed and no more than that. It is better to be a little in pain sometimes then being dizzy due to medication." P2*	alleviate pain. Distraction was used by all participants while the use of other methods was modest (massage in 25% and heating pad in 3% of observations).	frequently used non-pharmacological pain relief methods. This was concordant with the results of pain diaries showing that all children used non-pharmacological pain relief methods. These findings are consistent with previous findings in childhood ALL that emphasised the parental need to control the disease and strive for a normal life (Earle et al., 2007).
	Relationship with families This subtheme illustrated the "teambuilding" process between parents' and HCPs.	*"Normally, I feel very safe. I notice at once when the nurse is new and lacks experience. It also feels unpleasant when there is a new doctor, who does not know my child´s history. P6"*	Across all participants who completed the app, pain was on average reported in 54% (SD= 28.77) of observations whilst 46% of pain intensity and frequency ratings were zero values, which represented no pain.	The qualitative findings highlighted a parental need for stability (e.g., child's condition and collaboration with HCPs). Effective communication between clinicians and families helped the families during the ALL experience, which supports the previous results of Bettle et al., (2018). Results from pain diaries showed that the participants most frequently completed the app when the condition was stable. This explanation is supported by the large number of zero-value pain ratings in the app representing no pain. However, pain was reported on average in 54% of

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				observations but the app did not provide information about the child's condition (e.g., cause of pain) during the study period. The app was completed whenever the participants chose to do it. This is something that HCPs could encourage children and their parents to do more. The combination of the qualitative and quantitative findings leads to the idea that the children's or parents' pain reports should be incorporated in HCPs' routine symptom assessment and in the future, patients's self-reports should interface with the electronic medical records. This would enhance the collaboration between the HCPs and families. Furthermore, it could provide a complete picture of patients' symptoms experienced both in hospital and at home, as previously suggested by Linder & Wawrzynski (2018).
	Decision making This subtheme highlighted the importance of	*"Older children are widely involved in their assessments and decisions. I think we always succeed in*	Children older than 10 were able to provide self-reports of pain characteristics, pain relief	Interview findings emphasised that HCPs wanted to encourage children to be involved in their pain management. However, HCPs most frequently involved children who could verbalise their needs, typically older children. In the quantitative study, children older than 10

Qualitative findings			**Quantitative findings**	**Interpretation**
Themes	**Subthemes**	**Data segment**	**Daily reports on pain (0-10 scales)**	
	children's empowerment. Children were encouraged to have some control of their own pain management.	*working together with older children." D3*	methods, activity and mood.	years were able to provide daily data on pain, pain medication, activity level and function. The assumption that completing the app might increase a child's or a parent's feeling of being involved in treatment decisions supported the findings from interviews. This data fits well with the conclusions of Quaye et al. (2019) that children's active participation in treatment decisions has been associated with various positive effects.
	Child-parent coping This subtheme demonstrated the benefit of helping families to build effective coping strategies. Both mothers and fathers	*"It must be something about the mindset and about limits, to try to push those limits. I remember one of them, he kept on trying to play badminton, it was important to him. I think it was a form of*	Pain significantly impacted on children's physical, social and emotional functioning. The participants reported a limitation of physical activity (mean 4.81), general activity (mean 3.37) and mood (mean 2.42).	Interview findings based on an equal number of participating mothers and fathers described similar informational needs and perspectives on a child's pain. Both mothers and fathers emphasised the role of coping strategies for a child's pain experience. The results of pain diaries supported the qualitative findings providing data about the impact of pain on a child's activity and mood. These findings might relate to the integrative pain model of parent and family factors in chronic pain and associated disability. In this model, Palermo and Chambers (2005) highlighted the role of parenting style and parental reinforcement on a

Qualitative findings			**Quantitative findings**	**Interpretation**
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	wanted to be informed and involved in their child's treatment. Both parents were important for a child's coping and adaptive behaviour. Parents and HCPs stressed that mood influenced coping and physical activity was an important pain relief method.	*pain relief. I mean try to get them off the bed to minimise their sickness identity. "D3*		child's pain behaviour. Furthermore, the findings in this study suggested that the children tended to adopt coping mechanisms that positively impacted their mood, which supports the previous results of Polizzi et al. (2015), showing that ALL required special efforts of adjustment.

The following section analyses convergence and divergence between qualitative and quantitative findings and seeks to triangulate potential explanations. The starting point of the discussion will be the themes and subthemes identified in the qualitative study.

8.2.1. Complexity of pain assessment

8.2.1.1. Signs of pain

The overall finding from interviews was that pain in children with ALL was mainly caused by treatments and chemotherapy toxicity was especially a frequently cited reason for pain. Treatment as the major source of pain in children with leukaemia is widely documented and results reported in this thesis are in line with existing literature (Ljungman et al., 2000; Van Cleve et al., 2004). The pain diaries did not collect data about the cause of pain (procedural pain or adverse effects of chemotherapy). However, as pain was reported once daily in the app, the researcher assumed that the ratings most likely reflected average daily pain rather than episodic pain and the reason for this pain is probably related to the adverse effects of chemotherapy. Furthermore, the wording of the questions in the app ("How is your pain today?") was more likely to get registration of longer lasting pain (e.g., adverse effects of chemotherapy) rather than brief periods of pain. The location of pain also supports this explanation (abdomen, legs, mouth/throat), as chemotherapy often causes mucositis and neuropathic pain in the legs (Moore & Groninger, 2013) so results from the data collection techniques are considered congruent. Leg pain, followed by abdomen, head, throat, back, mouth and anus pain were found to be the most common locations for pain as measured by the pain diaries (Van Cleve et al., 2004). Moreover, regular mentions of these sites throughout interviews suggests general convergence between datasets.

There is evidence that children experience various unpleasant symptoms throughout the ALL treatment pathway (Johnston et al., 2018). Several symptoms are closely related to pain such as constipation, nausea, mucositis, sensory disturbances and diminished muscular strength (Clarke et al., 2016) Muscular weakness in the legs is the most frequently reported symptom in pain dairies (90%). However, this symptom may be included in general fatigue, which is also reported in other types of severe illness (e.g. malignancy) (Johnston et al., 2018; Ljungman et al., 2000). Muscular weakness is easy to assess by children and their parents (which may explain its high prevalence) while the assessment of other symptoms like nausea depends on the child's age. Thus, children younger than five presented a lower prevalence of nausea, which is in line with the literature

(Dupuis et al., 2016). Interview data highlights that adequate pain assessment should also include the assessment of these symptoms and provide explanations for the impact of them on a child's condition. The fact that the quantitative data from pain diaries supports these results suggests convergence between data sets. Furthermore, these findings suggest a common understanding of the signs of pain and associated symptoms among children, parents and HCPs.

There were two key points in respect to divergence between the pain diaries and interviews. The first divergence noted regarded the prevalence of pain: data from pain diaries found that children with ALL (or their parents) frequently reported moderate or no pain. In contrast, in most of the interviews, parents and especially HCPs described distressing episodes of pain and indicated that some children experienced clinically significant pain for long periods. A potential explanation of this divergence is that the participants most likely completed the app when the condition was stable and not during serious complications (e.g., requiring admission to the PICU), where according to interviews children experienced the most severe pain. Another explanation is that there are common characteristics but there may not be a single pain trajectory. The trajectory of many life-threatening paediatric conditions often involves unexpected complications as well as plateaus of relative stability (Hockenberry et al., 2017).

Furthermore, the literature indicates that a child´s symptoms fluctuate over the duration of treatment, resulting in a widely variable individual response (Rodgers et al., 2019; Van Cleve et al., 2004). Therefore, children's pain may be best described by heterogeneous pain trajectories. A further explanation would be a memory bias in the interviews, meaning that participants' memories largely reflect the worst intensity of pain they remember (Morley, 2016; Redelmeier & Kahneman, 1996). In contrast, daily pain reports collected electronically provide a more accurate picture of pain regarding fluctuations in time and differences between individuals, which extends existing knowledge about pain in ALL.

The second divergence between datasets regarded the level of pain intensity and frequency experienced by children of different ages. Thus, data from pain diaries demonstrated significantly higher pain intensity and frequency in children younger than ten compared to older children ($p < 0.001$), while interviews found that older children reported more pain. The literature describes a discordance between the child´s age and symptom intensity. Some studies suggested higher levels of pain and distress in older children compared with younger children (Getz et al., 2018; Van Cleve et al., 2004) while others found that younger children reported higher pain scores (Badr et al., 2006). A possible explanation of this finding is, as mentioned in the previous paragraph, the

difference between the memory bias in interviews and the accuracy in real-time self-reports (Morley, 2016). Another explanation may be that the parents of children younger than 10 years completed the app and reported their own perception of their child's pain. Full concordance between a child's and parents' reports of pain cannot be expected as the parents do not experience the same as their child. However, in paediatric oncology, parental proxy symptom report has been commonly used in children unable to report the pain due to young age or illness (Baggott et al., 2014). Collins et al (2000) and Zernikow et al (2005) reported a good agreement between a child's and parents' report. When no pain was reported, the child's and parents' assessment concurred on 91% of the time (Zernikow et al., 2005). However, Zhukovsky et al (2015) reported significant differences between reports of adolescents and their parents. Child-parent interactions may differ with parents of young children spending more time with their child, which provides more opportunities to observe their child's condition and develop abilities to report their pain (Cheng et al., 2018).

A further explanation may be that parents and HCPs interpreted older children and adolescents' psychological distress as physical pain. The use of behavioural cues for pain assessment has been widely reported in paediatric oncology with withdrawal and introversion often described as a sign of pain (Woodgate & Degner, 2003). Older children and adolescents may experience a variety of thoughts and emotions because they can understand the implications of their disease and consequently express more distress (Linder & Wawrzynski, 2018). In contrast, younger children report more physical and fewer psychological symptoms (Cheng et al., 2019). Furthermore, parents' and HCPs' pain assessments are frequently based on children's self-reports. Although children as young as four can provide self-report of their symptoms, barriers to eliciting young children´s self-reports remain (Woodgate & Degner, 2003). Most self-report measures have higher accuracy with older children as children's cognitive development affects the precision in measuring and interpreting pain experience (Tsze et al., 2013). In addition, young children may have difficulties describing the presence of multiple symptoms (e.g., pain and nausea) and may use expressions that may not be fully understood by HCPs. As a result, pain may go unrecognised and be inadequately managed (Twycross, Parker, et al., 2015). These findings support the explanation that regardless of developmental stage, pain is a unique individual experience, as described by one of the clinicians:

"It is difficult every time. Every single time. Each story is different." N3

Given that the pain trajectories are unique individual experiences and the memory of pain and other symptoms is often poor, the real-time self-reports of pain can provide accurate data about pain

patterns and changes over time. Therefore, the findings in the current work contribute to existing knowledge about the usefulness of real-time self-reports and the need for placing a greater emphasis on incorporating the child's voice whenever possible.

8.2.1.2. Getting pain assessment right

Findings from interviews indicate that pain assessment in children with ALL was sometimes challenging for HCPs. Clinicians emphasised that frequent pain assessments and adequate documentation of a child's pain experience were crucial aspects to ensure optimal pain management (Bettle et al., 2018; Plummer et al., 2017). Especially nurses and doctors from PICU, who met the families in acute, stressful situations, emphasised the importance of a clear documentation of a child's previous pain experiences. Nevertheless, HCPs described that they used pain scales too infrequently. These findings suggest that further efforts to implement the use of pain scales in the clinical settings are needed. This may enhance children´s pain monitoring and HCPs' understanding of this pain.

In addition, HCPs were concerned not being able to effectively manage pain especially when working with patients with complex care needs. The available pain guidelines did not provide sufficient support when larger doses of opioids were needed than are recommended by guidelines. However, data from the pain diaries suggest the opposite, that most children with ALL achieved good pain relief when they reported pain. As mentioned previously, a possible explanation for this divergence is the difference between data collection methods: pain diaries reflect a child's daily reality with variable symptoms (Jibb et al., 2017) while interviews describe caregivers' views, which may focus on the most challenging past pain experiences (see above, Section 8.2.1.1). However, in children with a chronic condition, electronic pain reports may lack the sensitivity required to measure nuances of pain (Leahy et al., 2018). Due to the chronic nature of pain in ALL, parents have time to learn their child's unique pain expression and both children and parents develop their own methods to manage pain. Similarly, HCPs emphasised that during the course of treatment they learned their patients and identified personal behaviours and preferences when planning treatment (Linder & Wawrzynski, 2018; Quaye et al., 2019).

8.2.2. Anxiety and fear for the unknown

8.2.2.1. Pain as a mask for psychological distress

Analysis of interview data identified that insufficient management of pain and anxiety during past painful experiences were associated with higher anxiety levels in children (Chen et al., 2000). Furthermore, the interviews highlighted that problematic family functioning and high levels of parental anxiety were associated with higher emotional and social impairment in children (Link & Fortier, 2016). Moreover, parental anxiety could lead to discrepancies between the families' and HCPs' understanding of the child´s illness and severity of symptoms (Rosenberg et al., 2014). Data from pain diaries support the fact that parental anxiety and distress are higher during acute changes in their child's condition (e.g., complications and involvement of other specialists and departments) as missing data occurred mainly during these situations. When the child was seriously ill and even unconscious, the parents experienced an increase in caring responsibilities and concerns. These challenges were associated with a reduced parental ability to cope with activities that were not directly treatment-related (Molinaro & Fletcher, 2018). Moreover, the parents were understandably protective of their children and consequently not always prepared to involve them in research (Colville, 2012).

However, children and their parents could only benefit from the symptom self-monitoring provided in the app when they completed it. Most of the parameters that participants reported in this study (e.g., pain, nausea, constipation) have prompts for the HCPs within the electronic health record of the hospital. The inclusion of the app self-reports in the existing documentation system would, most likely, have increased the participants' motivation to complete the app and the usefulness of the application for both patients and HCPs (Leahy et al., 2018).

8.2.2.2. Parental concerns about strong medication

Consistent with existing literature, the findings from interviews identified that despite concern and a desire to relieve, an aggressive approach to treating pain was often met with reluctance by parents (Turner-Cobb, 2014b). For parents, the use of "morphine" or "methadone" was difficult to accept due to social, cultural, and familial beliefs about illness and drug addiction. According to Friedrichsdorf and Kang (2007), the myths and obstacles associated with parental reluctance to use opioids for pain control include fear of giving up, misconceptions of opioids as "too strong for

children", fear of side effects, cultural and religious beliefs and worries that their child would become addicted to pain medications.

After two weeks or more of taking opioids, the body develops a physical dependence and the patients need to be weaned off opioids so they can adjust and avoid unpleasant withdrawal symptoms. In this research study, parents worried about all aspects of drug-taking: the physical dependence, the psychological dependence and the social stigma of addiction as a disorder characterised by the compulsive use of a substance (Smith et al., 2013). Furthermore, all parents reported uncertainty and misconceptions regarding the safety of opioids and fear of adverse effects. Those parents who had negative attitudes about analgesic use in children provided their children with fewer analgesics. This is consistent with the results of Fortier et al (2012) who found that parental negative attitudes towards analgesic medication were a significant predictor of the actual behaviours involved in a child´s pain management. However, most parents had changed these attitudes over time as parents learned more about their child´s disease and gained confidence in using pain medication to relieve their child's pain (Tutelman et al., 2018). Instead of attitudinal barriers towards pharmacological pain relief, the interviews identified a parental need to control pain medication and its adverse effects (e.g., using antiemetics and laxatives) (Earle et al., 2007). However, throughout the course of the disease, the parents associated the use of morphine with a more severe illness and wished to reduce its use as soon as the child's condition permitted it (Flemming, 2010).

Pain diaries and interviews converged regarding what parents did to manage their child's pain. Data from pain diaries demonstrates that the children had a limited use of analgesic medication, which is in accordance with the literature (Plummer et al., 2017). Participants used non-pharmacological interventions with distraction being the most frequent method, followed by massage and heating pads. These techniques were referenced in the interviews where parents reported a preference for non-pharmacological interventions (Tutelman et al., 2018). A potential explanation of this convergence is that the participants reported no pain in many ratings during the participation time. Furthermore, this convergence led to the idea that although parents may under-medicate their child's pain, they do not fail to respond. Instead, parents respond to their child's pain using a variety of non-pharmacological interventions.

In addition, the results of pain diaries document that pain intensity and frequency levels as well as the administration of analgesics tended to increase before complications, indicating that more

intense symptoms prompted parents to evaluate and react to changes in their child's condition. Teaching parents about pain and how to use a pain assessment instrument may impact on their knowledge and attitudes toward pain (Bettle et al., 2018; Huth et al., 2003). These findings extend knowledge about parental ability to evaluate and relieve their child's pain.

8.2.2.3. Clinicians concerns and uncertainty

Analysis of interview data identified that parental anxiety and family conflicts influenced the collaboration with HCPs. The reaction of some families to anxiety was sometimes an intense focus on their child's pain and request for stronger pain medication. Both nurses and doctors were cautious in such situations, especially when children requested higher doses of opioids than HCPs considered the children needed. HCPs were concerned about the adverse effects of treatments, the etiology of pain and the most appropriate therapeutic strategy. HCPs felt the need to make a distinction between administering opioids to relieve physical pain and administering opioids to reduce anxiety and distress. HCPs emphasised that minimising the level of distress (e.g., with analgesics) had a positive impact on children's pain, sleep problems and activity level. However, differences in perceptions of treatment strategies and goals between staff and families (e.g., expected level of pain relief) was sometimes perceived as leading to conflict, making HCPs feel culpable about their inability to achieve parental understanding. Results from the literature indicate that, when present, agreement between parents and HCPs expectations regarding symptoms and treatment is associated with better patient quality of life and improved care (Woodgate & Degner, 2003). Therefore, clarity of communication about the specific therapeutic course planned for a child may lessen the risk of families refusing a recommended treatment or not cooperating with the HCPs (Levine et al., 2019; Polizzi et al., 2015).

8.2.3. Empowering families

8.2.3.1. Relationship with families

Findings from the current work are in agreement with previous research suggesting that a collaborative relationship and effective communication between HCPs and parents help families navigate through the experience of ALL (Bettle et al., 2018). However, in the current research both parents and HCPs described their relationship as fragile, it could rapidly worsen when a child´s condition changed or if a high turnover of staff took place. This finding further supports the

importance of HCPs' skills to provide clear communication with parents (Ljungman et al., 2003; Rodgers et al., 2016). Although HCPs emphasised that the responsibility for treatment was with the clinicians and tried to protect the parents from this burden, they encouraged and empowered the parents to manage their child´s pain and associated symptoms. This was in line with parental needs to be fully informed and involved in treatment decisions. Empowering parents with the knowledge and tools they needed to manage their child´s pain might make them feel confident about their ability to improve their child´s well-being (Tutelman et al., 2018). This positive feeling of control might support their collaboration with HCPs during a child's illness.

8.2.3.2. Decision-making

The findings in this research indicate that children's active participation in decision-making was preferred by all participants across Study 1 and 2. Interviews highlighted that both parents and HCPs recognised the child as an individual capable of taking part in situations within its own competence (Linder & Wawrzynski, 2018). Also, results from pain diaries indicate that through the process of self-reporting, children learned to quantify their perception of pain, activity and mood and what they did to relieve pain. Being able to assess and self-report pain is an important step in developing the ability to participate in decision-making. This is to be welcomed, as children's active participation in decisions regarding their own treatment has been associated with decreased anxiety, increased sense of value and control, improvements in psychological and physical recovery, increased cooperation with procedures and improved perception of treatment services (Quaye et al., 2019). HCPs have a legal responsibility to ensure the best available childcare and that the rights, dignity and safety of the children are upheld during their hospital stay. Therefore, involving children and parents in the decision-making process is crucial during ALL treatment and is based on the HCPs' ability to understand and interpret a child's experiences.

8.2.3.3. Child-parent coping

In this research, there were no indications of gender differences in parental perspectives on their child's pain or how parents expected to be informed and involved in their child's treatment. Mothers and fathers seemed to act as members of a team who shared concerns and responsibilities. These results suggest that individual parental resources are more important for coping than gender related issues. In this context, both parents were important for a child's ability to cope and adaptive behaviour (Hill et al., 2009; McGrath & Chesler, 2004a). Findings from interviews suggest that a

child's ability to cope had a major influence on his/her pain experience (Enskär, Carlsson, Golsäter, et al., 1997). This seems to be supported by pain diaries, which indicate that although children (or their parents) reported reduced physical activity, they participated in other activities and their mood was often good. These findings suggest that, despite high post-diagnosis distress and painful experiences, children tend to react by adopting coping mechanisms, which have a positive influence on their mood (Myers et al., 2014; Polizzi et al., 2015; Sawyer et al., 2000).

8.3. Strengths and limitations

8.3.1. Strengths

This research study investigates the experience of pain and its management during childhood ALL from the perspective of a child, parents and clinicians.

A strength of this research study is that multiple perspectives are available (children, mothers and fathers as well nurses and doctors from the paediatric oncology department and PICU), which enable a comprehensive exploration of a child's pain in ALL. Parental perceptions and knowledge of their child are essential in the detection and interpretation of a child's experience of pain. Pain may be associated with emotional distress for the child and parents and parents' expectancies about a child's pain mediate between children's expectancies about and actual pain (Liossi et al., 2007). It is reasonable to assume that when a parent perceives that a child experiences pain, it has an impact on the parents, and consequently on the child's psychosocial function and parental understanding of this function (Palermo & Chambers, 2005). The dyadic perspectives of children and parents have been previously investigated in paediatric oncology (Baggott et al., 2014). Also, the nurses' experiences with children (Linder & Wawrzynski, 2018) and their parents (Bettle et al., 2018) have been previously explored. However, there are only a few studies that focused on doctors' experiences with paediatric patients and parents (Levine et al., 2019). Furthermore, previous studies have only investigated the perspectives of clinicians from a single medical specialty (e.g., paediatric oncology) (Forsey et al., 2013). In addition, the inclusion of an equal number of mothers and fathers of children with ALL is a strength as most paediatric oncology research represents maternal perspectives (Molinaro & Fletcher, 2018) (Section 5.3.1).

Another strength is that the child's voice is captured in pain diaries on a mobile application collected over the course of the first three months of ALL treatment, capturing pain both in-hospital and at home (section 7.3.1.). This surveillance time is longer than in other studies focusing on pain reports on a mobile application in children with cancer (Jibb et al., 2017; Leahy et al., 2018). a

Although a long surveillance time negatively impacts the completion rate ((Morren et al., 2009), the completion rate in the quantitative study was relative high (57.8%).

Moreover, the development of the How-R-you app was driven by expert paediatric anaesthetist and oncologist opinion as well as patient involvement to enhance the clinical relevance of this research (Section 6.2.2). The envisioned benefit of using How-R-you app was to give children and parents a tool for continually monitoring the child's state of health in contrast to only assessing it at fixed points in time (Van Cleve et al., 2004). The simple design of this app facilitated data collection that could reflect the wide age-span of clinical occurrence of ALL (Toft et al., 2018). In this research study, parents of children younger than 10 years completed the app while children older than 10 provided their own data. Involving children in self-reporting pain is increasingly emphasised in the literature (Leahy et al., 2018; Turk & Melzack, 2011). Moreover, involving patients and parents in a process of monitoring their own/their child's state of health enhances their self-confidence and abilities to manage this disease (Bettle et al., 2018).

A further strength of this research is that it seeks to investigate pain through triangulation of qualitative and quantitative findings. Mixed quantitative and qualitative approaches may provide a more comprehensive understanding of complex symptoms experienced by children with cancer. For example, chemotherapy-related fatigue was investigated in interviews with parents and questionnaires with parents and children (Whitsett et al., 2008). In this research study, the findings from interviews with parents, nurses and doctors facilitated the understanding of the results of pain diaries. Similarly, the examination of pain characteristics and the use of pain relief strategies reported in pain diaries by parents of young children or self-reported by children older than 10 years supported the interpretation of findings in interviews with parents and HCPs.

8.3.2. Limitations

One limitation of this research study is that the qualitative data was collected at one single treatment centre. Investigations at other treatment centres could have revealed other institutional practices such as the use of guidelines or pain assessment traditions. However, all Danish tertiary hospitals that conduct specialist treatment of childhood leukaemia use national guidelines for paediatric pain assessment and management. Furthermore, the current leukaemia treatment protocol is followed in 14 European countries including Denmark (Heyman et al., 2018). Although local traditions and preferences for different analgesic medication exist, it is most likely that patients and HCPs face

similar challenges during ALL treatment without any major disparities in pain control (Getz et al., 2018; Jensen, 2015).

Another limitation is that this research study does not provide information about the setting where the participants experienced pain (at home or in-hospital). Previous research concluded that children's cancer pain was not optimally managed in the home setting (Fortier et al., 2014) (section 7.3.2.). However, in this doctoral research the qualitative findings revealed that the children experienced more severe pain during hospitalisation and especially during admission to the intensive care unit. Although parents preferred the use of non-pharmacological pain relief methods, they gave their child analgesic medication while they were at home and called the hospital when they needed advice. The quantitative results support these findings demonstrating that the children received pharmacological and non-pharmacological pain relief on most occasions when they (or their parents) reported pain and that pain relief strategies reduced that pain. Although this research did not identify possible differences between pain management at home and in-hospital, the findings documented that the parents responded to their child's pain using various pain relief methods. However, the application of these methods depended on the parental beliefs and knowledge about pain, which supports previous studies about parental management of a child's pain (Fortier et al., 2012; Tutelman et al., 2018). The implication of these findings is that communication between HCPs and parents should include and address the presence of these beliefs and provide individually tailored information about pain management.

Another possible limitation is that this research study focused on children undergoing active, intended curative leukaemia treatment. Therefore, long-term experiences with ALL (e.g., survivors' experiences) were not captured. However, the examination of leukaemia survivors was not the scope of the study. On the contrary, this study focused on the first periods of leukaemia treatment (induction and consolidation), which are the most stressful (Sawyer et al., 2000). A surveillance time longer than three months might provide more data about pain variations in ALL but a prolonged participation in a research study would be a considerable burden for distressed children and families (Molinaro & Fletcher, 2018).

The small number of participants in the quantitative study is a limitation. Despite numerous efforts made to collect data from children treated at all Danish tertiary hospitals, the difficulty of accessing this population was a major challenge (e.g., due to local resources). Furthermore, two patients

included in the quantitative study died shortly after inclusion, reflecting the challenges of conducting research in a small paediatric population with a malign diagnosis (Section 7.3.2.). The small number of participants in this study may account for a limited possibility to generalise the findings to other populations of ALL patients. However, the long surveillance time of pain and the relatively high completion rate of the app ensured a large number of observations (306 response sets) that provided a nuanced picture of children's pain and their use of pain relief strategies. Moreover, some findings might be generalisable after interpretation. For example, the fact that children younger than 10 years (according to their parents) experienced intense pain that was significantly higher than the pain reported by older children, draws attention to the personal and subjective aspect of pain experience (IASP, 2020). Thus, this research study documents that children with ALL aged 1-17 years can experience pain, which can be shaped by a range of biopsychosocial factors. Therefore, this research highlights the complexity of paediatric pain assessment and management and argues for the incorporation of a child's pain self-reports whenever possible.

8.4. Contributions to new knowledge

What is already known on this topic?

Pain is the most common symptom experienced by paediatric patients with ALL (Van Cleve et al., 2004). Pain is primarily treatment- related (adverse effects of chemotherapy or invasive procedures) (Ljungman et al., 2000). Paediatric pain can negatively affect the quality of life and result in child and family distress (Sawyer et al., 2000; Sung et al., 2011).

What does this research add to existing knowledge?

1) Depth and breadth to understanding a child's pain experience from the perspectives of the child, parents, nurses and doctors. 2) A daily picture of pain characteristics and the use of pain relief strategies during the first three months of treatment in childhood ALL. 3) Knowledge about the use of electronic symptom monitoring in childhood leukaemia. Each of these issues will be explored in more detail in the following section.

8.4.1. Understanding a child's pain experience from the perspectives of the child, parents, nurses and doctors.

This research constitutes the first Danish study to investigate the experience of pain and its management during ALL from the perspectives of the child, parents, nurses and doctors. Findings from interviews with parents and HCPs and pain diaries completed daily by parents of children younger than 10 years and children older than 10 years confirmed that pain in children with ALL is common and caused primarily by treatment. The most frequent pain locations (legs, abdomen, head and back) are similar to previous research (Van Cleve et al., 2004). It is important to generate similar findings in different settings to increase generalisability of the body of literature as a whole (Bryman, 2016; Polit & Beck, 2010). Therefore, these confirmatory findings are an important contribution to literature. This research additionally demonstrates that although most of the time children have moderate or no pain, all children experience episodes of clinically significant pain during their disease pathway. Moreover, this research study demonstrates that every child with ALL experiences his/her own pain trajectory due to different biological (e.g., developmental stage, disease course) and psychosocial factors (e.g., distress). This research adds knowledge on a national and international level to the understanding of children's pain experience in terms of course, location, and prevalence.

This research is the first to investigate the perspectives of nurses and doctors from a paediatric oncology department and an intensive care unit. Children with ALL experience repeated pain episodes which can be described as chronic (Sawyer et al., 2000). During a child's disease, HCPs at the paediatric ward learn about the child's individual pain expressions and develop collaborative relationships with the family (Bettle et al., 2018). This balance is challenged when the child's condition is aggravated and the child is admitted to PICU. The findings in this research study support the conclusions of Colville (2012), who described that the intensive care specialists meet the child and family in a situation characterised by multiple invasive procedures and increased requirement for pain control. Although HCPs in PICU and paediatric oncology departments had similar perspectives on the multiple factors that influence a child's pain experience, HCPs in PICU emphasised more the importance of a child's and parents' past pain experiences. PICU clinicians indicated that knowing how a child and family coped with pain before the admission to PICU would increase their understanding of the child's pain experience. Furthermore, teaching the child and parents pain coping strategies at the onset of ALL would be beneficial throughout the treatment

pathway. This research study revealed physical and emotional experiences of children with ALL and their parents during the most distressing periods of their disease pathway that could not have been described without including the HCPs from PICU. These findings have implications for practice in terms of the importance of providing individually tailored information to families and documenting this information in the medical records. Furthermore, a multidisciplinary awareness and dialogue about the coping strategies of the child and family may enhance the collaboration between HCPs and parents across departments.

Research in this thesis adds knowledge about the experiences of mothers and fathers in childhood ALL. Including the perspectives of both mothers and fathers equally, this research study sought to provide a balanced parental perspective. The participating mothers and fathers described similar concerns and perspectives on their child's pain. Furthermore, mothers and fathers had high informational needs and wanted to be involved in their child's treatment. Previous paediatric research has mainly focused on maternal roles and influences on children with leukaemia (Earle et al., 2007). Other studies have targeted both parents, but maternal participation was dominant (Bettle et al., 2018). Although some research suggests that fathers want to engage themselves in childcare and treatment decisions there is a paucity of research that focuses equally on mothers and fathers of children with severe conditions (Hill et al., 2009; McGrath & Chesler, 2004a). Therefore, this research study develops literature by providing a missing father perspective.

8.4.2. The assessment and management of pain

This research study is the first to combine the investigation of a child's pain experience measured quantitatively on a mobile application with a qualitative exploration in interviews with parents and clinicians. Previous quantitative research measuring children's symptoms focused on prevalence and intensity (Dupuis et al., 2016; Hockenberry et al., 2017; Van Cleve et al., 2004). Had this research used solely quantitative methods to measure the children's pain, similar conclusions may have been reached. However, quantitative measures lack sufficient nuance to accurately detect differences between children's pain expressions, provide important information about the role of others and/or context in relation to the perception of pain. Due to the combination of data collection methods, this research was able to explain differences and similarities between a child's reports of pain and parents' and clinicians' views on that pain. In this context, this research outlines the impact of physical and psychosocial aspects of pain on its assessment and management.

This research study is the first to use a pain diary on a mobile application designed with experts in paediatric oncology across Nordic and Baltic countries. Moreover, this pain diary was tested by children with ALL and refined in a pilot test at a Danish hospital to capture possible nuances in pain expression and experiences in Danish children, who were included in this research study.

In addition, this research study is the first to describe how children with ALL report their daily pain during the first three months of ALL treatment (parent proxy reports of children younger than 10 years and self-reports of older children and adolescents). This surveillance time is longer than other studies based on pain reports on a mobile application in children with cancer (Jibb et al., 2017; Leahy et al., 2018) and contributes to new knowledge in the area of electronic symptom monitoring. The daily app registrations during the first three months of ALL treatment provided a more nuanced picture of a child's health, which could be used to monitor the child's condition and response to treatment. Electronic symptom monitoring is increasingly used in paediatric research and sometimes in clinical practice as it can potentially increase patient satisfaction and compliance. However, there are still important questions to be answered about this topic, such as selection of parameters, benefits to patients and integration to practice and existing electronic health records (Leahy et al., 2018) .

This research makes a unique contribution to the literature by describing pharmacological and non-pharmacological methods used to manage children's pain and the level of pain relief achieved by those children. In concordance with previous studies of Geeta et al (2010) and Tutelman et al. (2018), this research study found a moderate use of paracetamol (46% of pain ratings) and a low use of morphine (14% of pain ratings). Similar to those works, this research study lacks information about the setting where the children experienced pain (home versus hospital) (section 7.3.2.). However, findings in this study showed that children received pain medication on most occasions when they (or their parents) reported pain, which reduced pain intensity. Had this research investigated only pharmacological pain relief, it may have concluded in line with previous research, that parents were not attending enough to their child's pain and children were experiencing pain, which was being under-treated (Fortier et al., 2012).

In this research study, the findings from pain diaries support the interpretation of parents' and clinicians' pain assessment and management practices and can therefore contribute to existing

knowledge: parents do respond to children's pain by using a variety of non-pharmacological interventions together with pain medication. However, parents were hesitant to administer morphine due to worries that it would cause or exacerbate their child's fatigue, nausea or constipation. Moreover, parents associated opioids with complications and severe illness, while non-using non-pharmacological pain relief gave a sense of normality. Thus, this research suggests that the parents' and clinicians' understanding of a child's pain is essential for the use of pain relief strategies.

Additionally, this research measures the impact of pain in ALL on a child's function and demonstrates that pain has a substantial influence on a child's physical abilities. However, this research finds that exercise has a positive influence on a child's mood and that children attend different activities when their condition allows this. Importantly, the child's mood was often highlighted as good, although periods with emotional distress were also present. This is consistent with previous studies describing that a child's physical and emotional functioning improved over time during the ALL treatment (Earle et al., 2007; Sung et al., 2011).Thus, this research adds knowledge about the children's and parents' understanding of pain and strategies to cope with it, which sometimes contrast with clinicians' concerns of undertreatment. These findings emphasise the importance of studying multiple perspectives on a child's pain experience.

8.4.3. Methodological contributions to new knowledge

This research study is the first to consider the perspectives of parents, nurses and doctors in combination with a daily longitudinal exploration of a child's voice. Methods used in this research were inspired by the biopsychosocial models of pain aiming to take a holistic approach to understanding this topic (Liossi & Howard, 2016). For example, the role of a child's developmental stage on a child's expression of pain and the parents' and HCPs' response to this pain can relate to the social communication of pain model (Riddell et al., 2013). Using a mixed methods approach, this research has confirmed that complex phenomena such as a child's experience and management of pain during ALL, can be investigated within one research study. By investigating different aspects of this topic in a single study, relationships between aspects and interpretations of findings could be made, which would not have been achieved had a single method of data collection been used (Zhang & Creswell, 2013). This has implications for future researchers, who may choose a mixed methods approach when aiming to study complex phenomena.

8.5. Implications for clinical practice

Findings from this research point to the need to build capacity to support child-centred pain assessment and management, such as pain education for parents and HCPs. Pain trajectories in ALL are unique individual experiences. However, neither this research study nor the wider literature has ascertained a way of predicting which children will follow particular pain trajectories using clinically available information. Therefore, the emphasis needs to be placed on educating families about pain relief strategies and incorporating the child's voice whenever possible. Physical assessments, such as findings from pain scales do not always represent meaningful experiences for the child and family. Strategies that help HCPs obtain deeper insights into the child's perspective (both physical and emotional) may guide them to provide a better assessment and management of pain.

It would be helpful for clinicians to spend time talking at length with children and parents about their past pain experiences, as this can better support HCPs to work collaboratively with families to better manage a child's pain. Furthermore, acknowledging concerns and uncertainties during treatment for ALL may create opportunities for enhanced communication between families and HCPs. Understanding parental associations of strong analgesics with fear of severe illness and complications may facilitate the dialogue about a child's pain. Optimal pain management may include further development of shared broad relief strategies that include both pharmacological and non-pharmacological methods by both parents and HCPs.

Implementation of tools targeted to identify and tackle parental anxiety could be beneficial. It is important to focus on patients' and their families' needs when arranging psychosocial support and these needs should be continually reassessed throughout the trajectory of the illness. In addition, enhanced informational support is needed when the child's condition requires involvement of other specialists and departments.

Given the availability of new technologies and the ethical imperative to measure and improve patients' experiences and outcomes, it is relevant to investigate and implement these in practice. Therefore, involving broad sources of information, monitoring and communication can provide enhanced interaction with HCPs. Enabling more opportunities for patient and parental empowerment can potentially optimise pain management.

8.6. Recommendations & Future Research

The literature provides evidence that childhood ALL has high survival rates but patients experience multiple treatment-related distressing symptoms (Hockenberry et al., 2017; Pui et al., 2015). This research study has added knowledge about pain experience in ALL from the child's, parents' and HCPs' perspectives. In this section, the researcher makes following recommendations for future pain research in ALL.

Firstly, the use of innovative technologies to improve and increase the patient symptom-reporting process. The purpose of using symptom self-reporting is increased patient engagement in care, enhanced communication with HCPs and tailored individual symptom management (Leahy et al., 2018). In this era of personalised medicine, hearing and using a child´s voice will advance the ability to relieve pain and distress and improve outcomes. Future research could benefit from incorporating longitudinal self-reports in multicentre studies, which may improve the collection of data on less visible symptoms, such as pain, anxiety and distress, therefore providing better opportunities for enhanced supportive care.

Integration of patients' self-reports in existing documentation systems, such as electronic health records could enable real-time registration of individual responses to chemotherapy and other treatment strategies both in hospital and at home. However, this step will require careful selection of parameters which are meaningful for the patients and the clinical setting. Furthermore, implementation of these systems will require a change of culture among HCPs and a discussion of responsibilities and decision-making, especially when discrepancies between patients' and HCPs' assessments occur.

Secondly, the results of this study suggest a need for further research focused solely on a child´s pain and parental experience of that pain during a child´s admission to the PICU. This could provide a deeper insight into experiences during periods of time (days or weeks) when children experience severe pain and distress and often need high doses of opioids and sedatives. There are, however, many challenges relating to carrying out research with this population. It is usually not possible to talk to children admitted to PICU because they are critically ill, very young or have communication problems related to their medical condition. Furthermore, parents are highly anxious and understandably protective of their children and therefore not always prepared to involve them in research.

Finally, there is a need for continuous evaluation of practices focused on emotional assessment and support, as well as individually tailored information and the empowerment of children and families.

8.7. Reflexive perspectives: Being a researcher

My experience of this Professional Doctorate in Health programme has been fascinating and challenging. The development process has been complex and I felt encouraged to learn new skills and extend previously acquired knowledge. Reading, talking to peers, attending conferences and writing have been important steps during this doctoral research. In particular, writing about the methodological research approaches and their application to my project, as well as the interpretation of findings were both challenging and rewarding. This learning process has confirmed that continuous learning is a natural part of being a professional and there is still much more to learn.

The fact that my research topic focused on children, a vulnerable population, increased the complexity of the ethical issues. Ethical considerations played a central role for the choices I made during my research. For example, I started my research spending time at the paediatric ward to observe the staff and patients. Given the small number of children with leukaemia and doctors working with these children I found it difficult to describe my observations without breaking participants´ anonymity. Therefore, I decided not to include these observations in my research. However, I noticed that clinicians rarely included pain scores in their assessments, so I decided to focus exclusively on children's self-reports of pain in Study 2 (without clinicians' pain scorings as described in my first protocol). This shows that my study design developed during the research process due to new knowledge, circumstances and ethical considerations.

A new and fascinating area for me was the qualitative research. I particularly enjoyed the revealing experience of the interviews. I treasured the experiences that were communicated to me and I admired the participants' frankness in wanting to participate in healthcare research. After the experience of a lengthy process of transcription and coding, I finally got to the generation of themes and subthemes. This writing process of what goes on in the interviews was new and challenging for me but also rewarding to describe my own understanding of those participants' beliefs and views.

The experience of this doctoral research has taught me how important it is to keep my own opinion completely independent of the data being collected and only to interpret it carefully after a much thought and in-depth reading. My position as a doctor, who shared some knowledge of the situation with families and clinicians, had the potential to influence the analysis. I overcame this by

constantly returning to the data directly and discussing findings with my supervisors in our meetings. I appreciate how easy it is for one to impose one's beliefs and opinions and not be objective when interpreting the results. My case in point here is that I had started off with the belief (common for many clinicians and researchers) that children's pain was undertreated. However, although it seemed that the results from the interviews supported this perspective, I have also come to appreciate more the perspectives of children and parents and their ability to cope with pain and suffering. I think healthcare professionals need to listen to families and involve them as much as possible.

Working together with paediatricians, a software engineer and patients to develop a mobile application was an interesting experience. However, it was a demanding process to involve the specialists, present the research ideas at paediatric meetings, develop the current version of the leukaemia app and finally receive feedback from the Scientific Board of The Nordic Society of Paediatric Haematology/Oncology. This delay had a major influence on my final research planning. If the mobile application would have been developed earlier, I would have had the time to include several children in Study 2. Furthermore, I would have conducted the interviews with parents of children who had completed the app (to connect Study 1 and 2 as described in my first protocol). However, it could have been stressful for parents to participate in two studies regarding their child´s pain. Moreover, I do not believe that including the same parents in both studies would have significantly influenced the findings of my doctoral research.

Conducting Study 2 resulted in my reflection regarding many important aspects of conducting research including setting achievable, recruitment targets and the use of local gatekeepers to recruit participants. I learned that the target-setting of eligible participants in my research setup was too optimistic, as only one third of potential participants were approached. Approaching potential participants worked best at my hospital, most likely due to my frequent presence at the paediatric ward but it was not effective at the other Danish hospitals that were geographically dispersed hundreds of kilometres from each other. Although the project was supported by local paediatricians and organisations at these hospitals it did not guarantee the cooperation of individual gatekeepers. Therefore, I had several meetings and a continuous dialogue with the gatekeepers at different organisational levels to support their motivation. However, it was difficult for the staff to prioritise their resources to support the meeting of recruitment targets. In addition, I presume that despite broad information and technical support some HCPs might have been uncomfortable with new

technologies and due to this barrier, they chose not to involve their patients in a digital based research study.

I also learned that the rapid development of digital technology was an important aspect in planning research studies based on this type of collection tools. For example, an app may need several changes during a study performed over several years and this may have implications for data analysis and interpretation.

Furthermore, during the quantitative study I also learned that asking participants to register something manually during a long surveillance time, required patients to be highly motivated. It was even harder for the children with ALL and their families to keep up the requirements of completing app data over time. The first months after ALL diagnosis represented a difficult time with a high level of distress, pain and fatigue. Also, very sadly there was the issue of bereavement in terms of reducing sample size. I will focus on motivating strategies in my future projects.

Leukaemia is a rare but not a new disease. Contributions to new knowledge are important but also findings that support and build upon previous research are essential because they extend current knowledge on this topic. Knowledge and technology develop rapidly and I believe there is a need for more research that listens to the patients' needs and experiences. Several topics related to health can be investigated from the patients' perspective and qualitative or mixed methods research can be suitable in various situations. Personally, I felt that using a mixed methods approach revealed a new way to interpret the quantitative and qualitative findings.

In summary, I believe that my interest in being a researcher has increased during this doctoral programme and I will continue to develop my knowledge and skills throughout my career. I intend to disseminate the findings of my research and generally advocate for an effective pain management and patient empowerment.

8.8. Conclusion

The research in this thesis used a mixed methods approach to investigate the experience of pain and its management during ALL from the child, parent and clinician´s perspectives.

Findings in this study confirm that pain in children with ALL is common and caused primarily by treatment. The most frequent pain locations are similar to previous research (legs, abdomen, head, throat, mouth, back and anus). This research demonstrates that most of the time, children have

moderate or no pain. However, most children have episodes of clinically significant pain during their disease pathway. In addition, children experience different fluctuating symptoms such as nausea, constipation, mucositis, sensory disturbances and muscular weakness. Pain and other symptoms are most distressing in the first months after diagnosis, confirming this initial period as one of great stress for families. These findings were obtained by real-time pain reports (reported by parents of children younger than 10 years while older children provided own data) collected during the first three months of treatment. In addition, interviews allowed data to be collected regarding pain episodes which may not have occurred during the pain diary period. Overall, the findings in this study demonstrate that children´s experiences with pain in ALL can be described as individual pain trajectories.

Results of this research provide important insights into how parents, nurses and doctors understand, assess and manage pain experienced by children with ALL as well as the challenges they face in relation to assessment. Findings demonstrate that pain assessment is complex due to a wide range of physical and psychosocial factors. These factors are related to ALL treatment but also to a child's developmental stage and families' experiences.

Participant responses confirm that in children, agreement between families and HCPs in symptom severity is more concordant for physical symptoms than for anxiety and emotional distress. Thus, this research found a discordance between children's and HCPs perspectives on pain intensity and frequency in different ages. Pain reported in pain diaries was significantly higher in young children while interviews found that older children experienced more pain. These findings demonstrate that, regardless of age, all paediatric patients with ALL can experience severe pain. Additionally, these results confirm that younger children are not fully capable of describing their pain experience while older children and adolescents can express their distress. Furthermore, these findings suggest that current pain assessment practices do not effectively differentiate psychological distress from physical pain and pain experience. This emphasises the need for regular pain assessments that incorporate a child's self-reports. Collecting self-reports on a mobile application is feasible and seems to provide reliable data on a child's pain, pain relief, activity and mood. However, pain diaries were not completed during severe complications (e.g., admission to the PICU), suggesting that this method is most suitable for patients with relative stable conditions.

There were seldom major differences between parental and HCPs' perceptions of a child's pain levels but these differences were challenging for both parents and HCPs. These differences were

usually associated with the child's and parents' anxieties. Parental anxiety was associated with solicitous behaviour, which influenced the assessment and management of pain and was a source of uncertainty and moral distress in HCPs. However, pain diaries indicated that most of time, children reported no pain or good/acceptable pain relief. This is a further argument to use self-reports in pain monitoring, as it may add new dimensions to HCPs' efforts and concerns to assess and relieve a child's pain.

This research found no differences in mothers' and fathers' perspectives on their child's pain. Regardless of parents' gender or a child's developmental stage, parental informational needs were high and family empowerment required individual tailoring. Parents associated their child's pain and need for strong pain medication with severe illness, whereas non-pharmacological pain relief strategies gave a sense of control and normality. Children's self-reports indicated that high pain intensity was followed by increased use of pain medication, suggesting that families understood the usage of analgesics and their responses to pain were relevant. These findings suggest that patient and family education is associated with better understanding of illness and treatment.

In summary, the research in this thesis demonstrates that a child's pain experience in ALL can be a complex problem to assess and manage. Every child, regardless of age, experiences his/her own sensory and emotional pain trajectory. Optimal pain management requires comprehensive assessments of a child and family and, whenever possible, children's self-reports. A continuous focus on professional pain education and implementation of evidence in practice is needed in the clinical settings.

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Appendix 1. Letter from Central Denmark Region Committee in Biomedical and Research Ethics

Regionshuset
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Dear Luana

Dato 04-07-2016
Sagsbehandler Annette Engsig
komite@rm.dk
Tel. +4578410185
Sagsnr. 1-10-72-6-16

Thank you for your email in which you ask if your study "The parents and clinicians' experience with pain in childhood ALL" shall be notified to The Central Denmark Region Committees on Health Research Ethics.

According to the Act on Research Ethics Review of Health Research Projects, Act number 593 of 14 July 2011 section 14 (1) only health research studies shall be notified to the Committees. The Committees do not consider your study to be health research study (section 2 (1)) and therefore the study shall not be notified to the Committees.

Kind regards

Annette Engsig

Annette Engsig
Secretary

The Central Denmark Region Committees On Health Research Ethics

Appendix 2. Approval from Data Protection Agency in Central Region Denmark Study 1

Regionshuset
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midt
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Dato 26-10-2016
Sagsbehandler Helle Nikkel
Forskningsprojekter@rm.dk
Tel. +45 7841 0188

Vedrørende projektet: Smerte hos børn med leukemi. Forældrenes og sundhedsprofessionelles erfaringer.

Sagsnr. 1-16-02-579-16

Ovennævnte projekt er den 24-10-2016 anmeldt til Region Midtjylland. Der er samtidig søgt om tilladelse til projektet.

Det fremgår af anmeldelsen, at du er projektansvarlig for projektets oplysninger.

Behandlingen af oplysningerne ønskes påbegyndt den 16-01-2017. Data slettes, anonymiseres eller indsendes til Rigsarkivet senest ved projektets afslutning.

Oplysningerne vil blive behandlet og opbevaret fysisk på følgende adresse:

Luana Leonora Jensen
aflåst lægekontor, Operation og Intensiv Syd, K-anæstesi
Aarhus Universitetshospital, Skejby
Palle-Juul-Jensens Boulevard 99
8200 Aarhus N

Projektet omfatter ikke en biobank.

Tilladelse
Der meddeles herved tilladelse til projektets gennemførelse.

Der gives alene tilladelse til behandling af lovligt indsamlede oplysninger, og under forudsætning af, at alle øvrige nødvendige tilladelser er indhentet, herunder eventuelle skriftlige patientsamtykker.

Region Midtjylland fastsætter i den forbindelse nedenstående vilkår.

Appendix 3. Interview topic guide with parents

Topics in the interviews:

- the usefulness of available guidelines
- the professionals' management of knowledge and management of severe pain conditions
- experience with assessment and documentation of pain and pain types

Questions:

1. Tell me about you and your child.
2. When do you think your child is in pain?
   Prompts: What signs of pain do you look out for?
   a. What symptoms do you look out for?
   b. What emotions or other behaviours do you look out for?
   c. What does distress look like?
   d. How can you see the child's coping?
   e. What do you mean he/she is good at coping?
3. How do you evaluate pain?
   Prompts:
   a. Can you describe how you can see different types of pain?
   b. Can you describe how you assess the severity of pain?
   c. Is there anything that influences your assessment?
4. Are you or is your child involved in documenting pain experiences?
5. What challenges do you experience in assessing pain in your child?
6. How do you see the nurses' roles in that impact?
7. How do you see the doctors' roles in that impact?
8. Can you describe to me how /when you/your child asks for pain relief?
9. How do you decide what pain relief to ask for?
10. Can you tell me about pain medication?
    Prompts: Is there anything your child prefers? Is there anything that is uncomfortable?
11. Does your child use anything else to relieve pain?
12. Tell me about a special situation you remember.

13. We´ve come to the end of my questions, is there anything else you think is important on this topic that we haven´t covered?
14. Do you have any questions for me?

Appendix 4. Interview topic guide with healthcare professionals (doctors and nurses)

Topics in the interviews:

- the usefulness of available guidelines
- the professionals' management of knowledge and the management of severe pain conditions
- experience with assessment and documentation of pain and pain types

Questions:

1.Tell me about your role in providing care for children with leukaemia.

2. How often do you work with children in pain?

3. When do you think a child is in pain?

Prompts: What signs of pain do you look out for?

f. What symptoms do you look out for?
g. What emotions or other behaviours do you look out for?
h. What does distress look like?
i. How can you see their coping?
j. What do you mean they are good at coping?
k. How can you know the parents are afraid?

4. How do you assess pain?

Prompts:

d. Can you describe how you assess different types of pain?
e. Can you describe how you assess the severity of pain?
f. Is there anything that influences your assessment?

5. What challenges do you experience in assessing pain in children?
6. How do you find documenting patients' pain experiences?
7. Are family members /the children themselves involved in documenting their pain experiences?
8. Can you describe to me how you decide whether to give pain relief?
9. How do you decide what pain relief to give?

10. Can you tell me about pain medication guidelines?
11. Can you tell me about other knowledge or resources you use when caring for children in pain?
12. We have come to the end of my questions, is there anything else you think is important on this topic that we have not covered?
13. Do you have any questions for me?

Appendix 5. Approval from the Central Denmark Region Committee in Biomedical and Research Ethics

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Dato 19-03-2018
Sagsbehandler Anja Skov Sørensen
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Sagsnr. 1-10-72-150-18

Projekt: Smerte og smertebehandling hos børn med leukæmi.

De Videnskabsetiske Komitéer for Region Midtjylland, Komité I, har behandlet projektet på sit møde den 13. marts 2018 og truffet følgende afgørelse.

Afgørelse:

Projektet godkendes i henhold til lovbekendtgørelse nr. 1083 af 15. september 2017 om bekendtgørelse af lov om videnskabsetisk behandling af sundhedsvidenskabelige forskningsprojekter.

Godkendelsen gælder for de anmeldte forsøgssteder, den anmeldte forsøgsansvarlige i Danmark samt for den angivne forsøgsperiode.

Godkendelsen gælder til den 15. marts 2020 og omfatter følgende dokumenter:

- Forsøgsprotokol, version 16. februar 2018, fremsendt per mail den 17. februar 2018.
- Deltagerinformation (til forældre), version 16. februar 2018, fremsendt per mail den 17. februar 2018.
- Deltagerinformation (til unge, som fylder 18 år under forsøget), version 16. februar 2018, fremsendt per mail den 17. februar 2018.
- Deltagerinformation (til store børn og unge), version 16. februar 2018, fremsendt per mail den 17. februar 2018.
- Samtykkeerklæring, version 22. januar 2018, fremsendt per mail den 2. februar 2018.

Iværksættelse af projektet i strid med godkendelsen kan straffes med bøde eller fængsel, jf. komitélovens § 41.

Ændringer:

Foretages der væsentlige ændringer i protokolmaterialet under

Appendix 6. Approval from the Data Protection Agency in Central Region Denmark Study 2

[redacted]

Regionshuset
Viborg

Regionssekretariatet
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Skottenborg 26
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Tel. +45 7841 0000
kontakt@rm.dk
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midt
regionmidtjylland

Dato 24-10-2017
Sagsbehandler Annette Engsig
forskningsprojekter@rm.dk
Tel. +45 7841 0188

Vedrørende projektet: Pain variations and management in childhood acute lymphoblastic leukaemia

Sagsnr.: 1-16-02-850-17

Ovennævnte projekt er anmeldt til Region Midtjylland.

Der er samtidig søgt om tilladelse til projektet.

Det fremgår af anmeldelsen, at du er projektansvarlig for projektets oplysninger.

Behandlingen af oplysningerne ønskes påbegyndt den 01-01-2018.

Data slettes, anonymiseres eller indsendes til Rigsarkivet senest ved projektets afslutning.

Oplysningerne vil blive opbevaret eller behandlet på følgende adresser:

1. Hospitalsenheden Horsens
   Anæstesiologisk afdeling
   Sundby 30
   8700 Horsens

Oplysningerne vil blive behandlet i samarbejde med følgende myndigheder eller virksomheder:

1. Aarhus Universitetshospital
   Børn og Unge
   Palle Juul- Jensens Boulevard 99
   8200 Aarhus N

Projektet omfatter ikke en biobank

Tilladelse

Der meddeles herved tilladelse til projektets gennemførelse.

Der gives alene tilladelse til behandling af lovligt indsamlede oplysninger, og under forudsætning af, at alle øvrige nødvendige tilladelser er indhentet, herunder eventuelle skriftlige patientsamtykker.

Region Midtjylland fastsætter i den forbindelse nedenstående vilkår.

Tilladelsen gælder indtil den 31-12-2022.

Projektanmeldelsen vil henhøre til Region Midtjyllands generelle anmeldelse til Datatilsynet,

Appendix 7. Information sheet for parents

Title of project: Pain variations and management in childhood acute lymphoblastic leukaemia.

Thank you very much for considering taking part in this study. Before you decide if you and your child can take part in this study, it is important that you understand why this study is being carried out and what it will involve. Please take the time to read this information carefully, and contact me if anything is unclear or if you would like more information.

If you decide you and your child would like to take part in this study, you will be asked to give informed consent.
Please note, your child's participation in this study is voluntary and you and your child are free to withdraw from the study at any time.
Whether your child participates in this study or not, all treatments your child receives in this department will continue and nothing will change.

Background for this study

Acute Lymphoblastic Leukaemia (ALL) is the most common childhood cancer. Approximately 30 children and adolescents below18 years are diagnosed with ALL annually in Denmark. Children with ALL within the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) and two Baltic countries (Estonia and Lithuania) are treated according to a common chemotherapy protocol. Children with leukaemia experience different side-effects of chemotherapy. Pain and nausea are two of the most frequent symptoms. These symptoms may be difficult to describe by children and their parents. However, parental observations and children's answers are very important for the way nurses and doctors interpret and treat symptoms with pain medication, antiemetics or fluids.

We have previously tested an electronic pain diary (an app for smartphones and tablet devices) in the paediatric department, Aarhus University Hospital, Denmark. We have used the feedback from parents and children to develop and adjust this app. Our pilot test showed that an electronic pain diary is useful for parents and children to register pain and other associated symptoms in ALL.

What is the purpose of this study?

The aim of this study is to explore the variations and management of pain, captured on an electronic diary in children with acute lymphoblastic leukaemia.

Participants

Children aged 1-17 years newly diagnosed with ALL and their parents will be invited to participate in this study. These children will undergo treatment at paediatric oncology departments at the university hospitals in Copenhagen, Aarhus, Odense and Aalborg. The study period is one year. Thirty patients are expected to be eligible during the study period.

How will this study take place?

Parents and children admitted with ALL at paediatric oncology departments will be introduced to the app during their first week of admittance and will be invited to participate in this study. After your written consent, you will be asked to complete the app (on your iPhone or iPad) once daily during the first three months of therapy.

The principal investigator in this study or the staff at the ward will show you, your child and family how the app works and how to assess and register your child's symptoms. Do not hesitate to contact us if you need further explanation. If your child is older than 10 years, he/she can complete his/her own data in the app.

We encourage parents to support their children to complete the app, especially when children are tired or have difficulties due to other conditions.

We would like to ask you to register pain, nausea, mucositis, constipation, muscular strength, the child's mood, the way your child walks, uses their hands and plays and the treatment your child receives.

We would like to ask you to register the symptoms during the first 3 months of the treatment because chemotherapy side-effects are most intense during this period of treatment. It will take approximately 5-15 minutes every day to complete the app. It is important for us that you register

every day even when you and your child have a difficult day. It is best you register at the same time of day, both in hospital and at home.

How will my information be stored/used in the future?

The data you and your child provide during this study belongs to you and you can use it to follow the treatment pathway. Participants will be identified using an ID code assigned by the study and no personal data will be stored. The investigator will load study data on a secure computer, where it will be treated as confidential and anonymity is assured in accordance with data protection rules. At no point will any data be associated with your child's name or identity.

What are the benefits of this study?

The potential benefits of this study are to extend the knowledge about a child's pain experience in leukaemia and use this knowledge to improve pain management.

Are there any risks?

There are no risks related to this study, as it will not have any direct influence on the treatment of participating children.

Are there any economic issues?

The participants in the study will not receive any compensation for completing the app.
The investigator has no economic benefits from this study and there are no conflicts of interests.

Who will review this study?

This study has gained approval from Danish Data Protection Agency and the Danish Committee on Biomedical and Research Ethics and from the Research Ethics Committee for Health at the University of Bath, UK.

Dissemination

Once the data has been analysed, it may be used in publications in academic journals and reports, but your child will not be identified at any point.

Principal investigator:

Luana Leonora Jensen, MD
Department of Anaesthesia and Intensive Care
Aarhus University Hospital, DK
Telephone: [redacted]
Email:[redacted]

Appendix 8. Information sheet for children and young people

Title of project: Pain variations and management in childhood acute lymphoblastic leukaemia.

Thank you very much for considering taking part in this study. It is important that you understand why this study is being carried out and what it will involve. Please take the time to read this information carefully, and contact me if anything is unclear, or if you would like more information.

What is the purpose of this study?

This study will explore the duration, intensity and management of pain in children with acute lymphoblastic leukaemia (ALL).

Children with leukaemia experience different symptoms related to their disease and treatment. Pain, nausea and fatigue are some of the most frequent symptoms. Clinicians involved in your care would like to expand their knowledge on these symptoms and improve their practice.

How will this study take place?

This study will be conducted at four Danish paediatric oncology departments, Copenhagen, Odense, Aarhus and Aalborg. Children and young people aged 1-17 years with newly diagnosed ALL will be invited to participate in this study.

The study comprises daily registrations of symptoms done by you on a pain app (on your iPhone or iPad). Your parents can do their own registrations on the app if they wish. Please note, nurses and doctors will assess your condition whenever this is required, regardless of whether you participate in this study or not.

The principal investigator in this study or the staff on the ward will show you and your family how the app works and how to assess and register your symptoms. We encourage schoolchildren and young people to register the symptoms by themselves so we can better understand your condition. Do not hesitate to contact the principal investigator if you need further explanation.

We would like you to register pain, nausea, mucositis (how sore you are in your mouth), muscular strength, the way you walk, use your hands and the way you manage your daily activities.

It is important that you register every day during 3 months of the treatment, even when you and your family have a difficult day. It is best you register at the same time of the day.

You will not be identifiable from the data you and your family provide as part of the study.
If you and your family decide to take part in this study, one of your parents or your legal guardian will be asked to give informed consent.

Please note, your participation in this study is voluntary and you are free to withdraw from the study at any time.
Whether you accept to participate or not, all the treatment you receive in this department will continue and nothing will change.

How will my information be stored/used in the future?

The data you and your family provide during this study belongs to you and you can use it to follow the treatment pathway. The investigator will load this data on a computer, where it will be kept confidential and anonymous in accordance with data protection rules. At no point will any data be associated with your name or identity. Once the data has been analysed, it may be used in publications in academic journals and reports, but you will not be identified at any point.

Who has reviewed this study?

The Danish Data Protection Agency and the Danish Committee on Biomedical and Research Ethics look at health research in Denmark.
This study is a part of a Professional Doctorate study at the University of Bath and has also been reviewed by the University of Bath Ethics committee.

What do I do if I am interested?

If you would like to take part in this study, please contact me or the staff in your department. If you would like further information or have any concerns, please contact me via the details below.

Principal investigator

Luana Leonora Jensen, MD
Department of Anaesthesia and Intensive Care
Aarhus University Hospital, DK
Telephone: [redacted]
Email:[redacted]

Appendix 9. Informed consent form

Title of project: Pain variations and management in childhood acute lymphoblastic leukaemia.

Principal investigator
Luana Leonora Jensen, MD
Department of Anaesthesia and Intensive Care
Aarhus University Hospital
[redacted]
Email: [redacted]

This is a consent form for you and your child to take part in this study.
You are giving consent to take part in the study by ticking all the boxes.

☐ I confirm that I have read and understand the information sheet for the above study.

☐ I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

☐ I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving any reason, without my legal rights being affected.

☐ I understand that any information collected during this study will be held confidentially.

☐ I understand that the outcomes of this study may be published and that individuals participating in the study will not be identified in any of these publications.

☐ I understand that this project has been reviewed by, and received ethics clearance through the Research Ethics Approval Committee for Health of the University of Bath

☐ I agree to take part in the above study

Print name and signature of participant: _____

Date: _____

Print name and signature of investigator: _____

Date: _____